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2. Dodd, K.: *J. Arkansas M. Soc.* **10**:174, 1954.
3. Hanbery, J. W.: *Neurology* **4**:301, 1954.
4. Miller, G.; Hansen, J. E., & Pollock, B. E.: *Am. Heart J.* **47**:453, 1954.
5. Keefer, C. S., in Smith, A., & Wermer, P. L.: Modern Treatment, New York, Paul B. Hoeber, Inc., 1953, p. 65.

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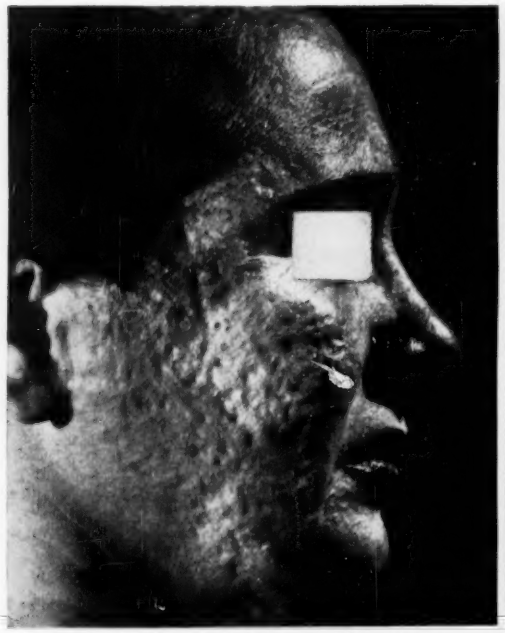

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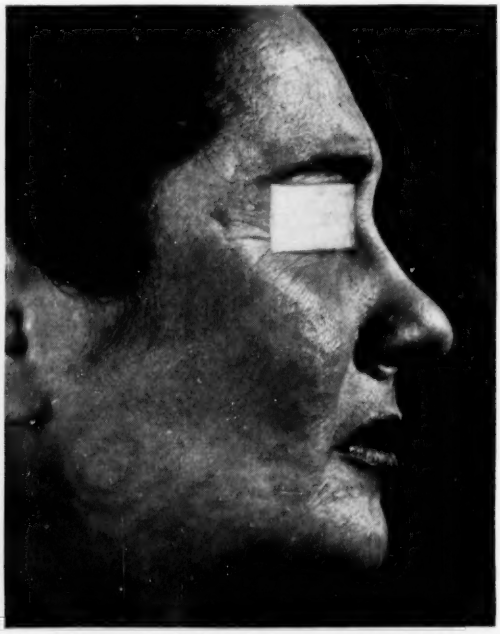

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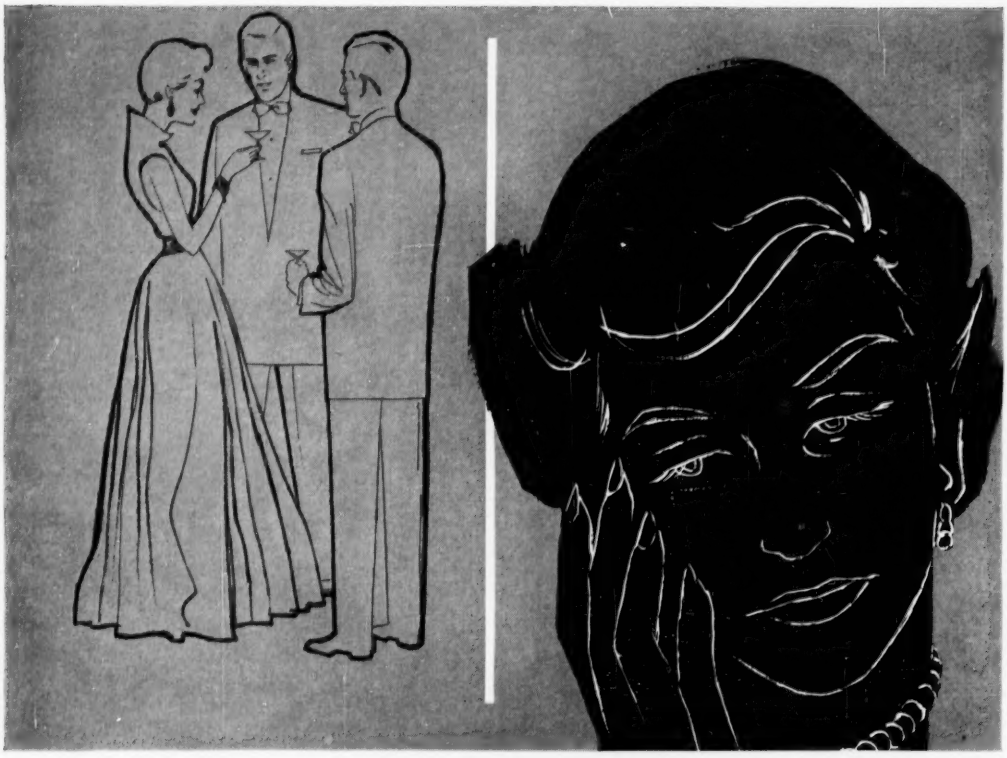

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COMBINED THERAPY IN HISTOPLASMOSIS AND COCCIDIOIDOMYCOSIS

Methyltestosterone and Meth-Dia-Mer-Sulfonamides

JOHN H. LAMB, M.D.
OKLAHOMA CITY

With the Collaboration of Gerbert Rebell; Phyllis E. Jones, M.D.; Robert J. Morgan, M.D., and John M. Knox, M.D.

THERE IS no reported instance of treatment of systemic fungous disease in man with testosterone compounds. In 1953 Lamb and his associates [1] reported the cure of a mycetoma caused by an atypical Nocardia under treatment with large doses of pregnenolone acetate. Trial of this steroid in disseminated coccidioidomycosis has been unsuccessful.* The use of aromatic diamidines structurally related to synthetic estrogens is being thoroughly investigated by Curtis and his co-workers.[2]

The present paper presents in vitro and in vivo laboratory studies of testosterone compounds as fungistatic agents and a report of the clinical trial of methyltestosterone and meth-dia-mer-sulfonamides (triple sulfonamides) in three cases of the deep mycoses.

LABORATORY ASSAY OF ANTIMYCOTIC EFFECT OF TESTOSTERONE COMPOUNDS AND SULFONAMIDES

In Vitro Assay of Testosterone, Methyltestosterone, and Testosterone Propionate.—In 1949 Reiss [3] demonstrated that testosterone, methyltestosterone, and other steroids and steroid-like compounds possess moderate fungistatic activity in vitro against Histoplasma capsulatum and other pathogenic fungi. Using a pour plate in vitro method described in a previous publication,[4] we have found testosterone, methyltestosterone, and testosterone propionate to be among the more fungistatic compounds of over 50 steroid compounds tested, concentrations of 0.01% producing complete fungistasis of Histoplasma capsulatum and Blastomyces dermatitidis and partial to complete fungistasis of Coccidioides immitis (Table 1).

In Vitro Assay of Methyltestosterone and Meth-Dia-Mer-Sulfonamides Combined.—Although sulfonamides cannot be said to be generally effective antimycotic

Read before the 74th Annual Meeting of the American Dermatological Association, Inc., White Sulphur Springs, W. Va., April 17, 1954.

Dr. Knox, formerly of Oklahoma City, is now in the Department of Dermatology, University Hospital, University of Michigan Medical School.

This investigation was made with the assistance of the National Cancer Institute, Dome Chemicals, Inc., New York; Eaton Laboratories, Inc., Norwich, N. Y.; Duke Laboratories, Inc., Stamford, Conn.; The Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association, and the Everett S. Lain Dermatological Fund of the Oklahoma Medical Research Foundation. Laboratory space was provided in the Dermatologic Section of the Oklahoma Medical Research Foundation Building.

*Wilson, J. W.: Personal communication to the author.

TABLE 1.—*In Vitro Effect of Testosterone Compounds*

Test Fungi	Strain	Test Dilutions, % Testosterone				Control Dilutions, % Acetone		
		0.1	0.01	0.001	0.0001	4.0*	0.4	0
T. mentagrophytes	1A3	+	+	++++	++++	++++	++++	++++
M. lanosum (M. canis)	2A4	+	+	++++	++++	++++	++++	++++
C. albicans	10A1	++++	++++	++++	++++	++++	++++	++++
C. neoformans	6A7	+++	++++	++++	++++	++++	++++	++++
B. dermatitidis	7A2	0†	0	++	++++	++++	++++	++++
H. capsulatum	9A10	0	0	+++	++++	++++	++++	++++
H. capsulatum	9A11	0	0	++	++++	++++	++++	++++
H. capsulatum	9A12	0	0	+++	++++	++++	++++	++++
C. immitis	11A2	+	+	++++	++++	++++	++++	++++

	% Methyltestosterone				% Acetone		
	0.1	0.01	0.001	0.0001	4.0	0.4	0
1A3	+	+	++++	++++	++++	++++	++++
2A4	+	+	++++	++++	++++	++++	++++
10A1	++++	++++	++++	++++	++++	++++	++++
6A7	++	++++	++++	++++	++++	++++	++++
7A2	0	0	++++	++++	++++	++++	++++
9A12	0	0	++++	++++	++++	++++	++++
11A2	++	++	++++	++++	++++	++++	++++

	% Testosterone Propionate				% Acetone		
	0.1	0.01	0.001	0.0001	4.0	0.4	0
1A3	+	+++	<++++‡	<++++	++++	++++	++++
2A4	+	+++	++++	++++	++++	++++	++++
10A1	++++	++++	++++	++++	++++	++++	++++
6A7	<++	++++	++++	++++	++++	++++	++++
7A2	0	0	+	++++	+++	++++	++++
9A12	0	0	+	<++++	++++	++++	++++
11A2	0	0	+	++++	++++	++++	++++

* 4.0 acetone control serves as control of 0.1% steroid test dilution only.
† 0 = no growth, ++++ = maximum growth, etc.
‡ <++++ = less than ++++ but greater than +++, etc.

TABLE 2.—*In Vitro Fungistatic Effect of Methyltestosterone and Meth-Dia-Mer Sulfonamides*

Fungus Strain	% Meth-Dia-Mer Sulfonamides	% Testosterone			
		0.01	0.001	0.0001	0*
B. dermatitidis, Strain 7A2	0.01	0	<<+++†	<+++	++++
	0.001	0	+++	<++++	++++
H. capsulatum, Strain 9A12	0.01	0	<+	<+	<+
	0.001	0	<++	++	++
	0.0001	0	++++	++++	++++
H. capsulatum, Strain 9A14	0.01	0	++	++	++
	0.001	0	+++	++++	++++
	0.0001	0	++++	++++	++++
C. immitis, Strain 11A2	0.01	+	++++	++++	++++
	0.001	++	++++	++++	++++

* 0.4% acetone control and higher dilutions of meth-dia-mer sulfonamides not included on chart.
† <<+++ = less than <+++ but more than ++; <+++, less than +++ but more than <<+++; <+, growth apparent only on microscopic examination of plates.

agents, they are known to exert some fungistatic effect in vitro,† and in more than one reported instance of true mycotic infection their clinical use has been accompanied by remissions.‡ Reports have been particularly frequent of the successful use of sulfonamides in paracoccidioidomycosis, histoplasmosis (cryptococcosis), and apparently localized histoplasmosis involving nonpulmonary lesions. The use of sulfonamides with testosterone in these diseases has not previously been reported. The in vitro effect of various combinations of methyltestosterone and meth-dia-mer-sulfonamides (sulfadiazine, sulfamerazine, and sulfathiazole) was determined by a modification of the technique described elsewhere,[4] using acetone as the primary steroid solvent and a 1% aqueous solution of sodium bicarbonate as the primary solvent for the sulfonamides (sterilization and solution were accomplished by autoclaving 10 minutes at 15 lb. [6.8 kg.] pressure). A slight fungistatic effect of the sulfonamides was observed, with no appreciable additive or synergistic effect with methyltestosterone (Table 2).

In Vitro Assay of Sulfanilamide.—Table 3 shows the in vitro fungistatic effect of sulfanilamide, with use of distilled water as the primary solvent.

Failure of Testosterone Compound to Control Experimental Histoplasmosis, Blastomycosis, and Coccidioidomycosis in Mice.—In vitro studies were made using male white Swiss mice, approximately 18 gm. in weight, obtained from the Maple Grove Rabbitry, Springfield, Mo., divided in groups of 20 and inoculated intraperitoneally with 0.1 ml. of a 1:100 volumetric suspension[4] of fungus elements in 5% gastric mucin (Wilson Laboratories). Five mice in each group received 0.1 ml. of an aqueous suspension of testosterone, 50 mg. per cubic centimeter (Shenley), subcutaneously (in the back) each day, beginning the day following inoculation and continued for the course of the experiment (one to four weeks). Five mice in each group received the same quantity of testosterone propionate in oil (Schering). Other mice were divided into control groups (Table 4). This technique failed to reveal an effect of testosterone propionate on the course of the experimental disease, manifest by a reduction of splenomegaly (Table 4) and amount of fungi in microscopic section of spleen and liver in histoplasmosis or a reduction in gross and microscopic lesions in coccidioidomycosis. It was thus concluded that under the conditions of the tests the steroid failed to convey protection to the mice inoculated experimentally with these two pathogenic fungi. In the case of mice injected with blastomycosis some effect was observed: (1) Mice receiving test steroid compounds and control oil injections developed significantly less infected nodular tissue in the peritoneal cavity than mice receiving control saline (Table 4); (2) a larger number of positive cultures were isolated from mice receiving saline or oil control injections than from those treated with testosterone compounds (Table 5).

Failure to Demonstrate Fungistatic Activity in Sera of Mice Receiving Testosterone Propionate in Oil.—Following a report by Tarbet and Sternberg,[11] we assayed the blood serum of mice receiving testosterone propionate for fungistatic activity. Pooled serum was obtained from each of three groups of 10 Strain C57 Brown mice, 5 male and 5 female, weight 18 to 20 gm., bred from stock obtained from the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine. The blood was collected into sterile petrolatum-lined tubes by cardiac puncture, after

† References 5 to 8.

‡ References 9 and 10.

TABLE 3.—*In Vitro Fungistatic Effect of Sulfanilamide*

Fungus Strain	% Sulfanilamide					
	0.1	0.01	0.001	0.0001	0.00001	0
1A3	+	++++	++++	++++	++++	++++
2A4	0	+	++++	++++	++++	++++
10A1	++++	++++	++++	++++	++++	++++
6A7	+	++++	++++	++++	++++	++++
7A2	+	++++	++++	++++	++++	++++
9A12	0	0	0	++++	++++	++++
11A2	0	++++	++++	++++	++++	++++

TABLE 4.—*Cultures Made After Testosterone Therapy, from Mice Infected with C. Immitis, H. Capsulatum, and B. Dermatitidis*

Mice Infected with C. Immitis

Mouse No.	Mice Receiving Testosterone Compounds		Mice Receiving Control Vehicles	
	Infected Nodule	Lung	Infected Nodule	Lung
1	No nodules	Negative	No nodules	Negative
2	No nodules	Negative	C. immitis	C. immitis
3	C. immitis	C. immitis	C. immitis	C. immitis
4	C. immitis	C. immitis	C. immitis	C. immitis
5	C. immitis	C. immitis	No nodules	Negative
6	C. immitis	C. immitis	C. immitis	C. immitis
7	C. immitis	C. immitis	C. immitis	C. immitis
8	C. immitis	C. immitis	C. immitis	C. immitis
9	No nodules	Negative	C. immitis	C. immitis
10	C. immitis	C. immitis	No nodules	C. immitis

Mice Infected with H. Capsulatum

Mouse No.	Mice Receiving Testosterone Compounds		Mice Receiving Control Vehicles	
	Spleen	Heart Blood	Spleen	Heart Blood
1	H. capsulatum	Negative	Negative	Negative
2	H. capsulatum	H. capsulatum	Negative	Negative
3	Negative	H. capsulatum	Contaminated	H. capsulatum
4	Negative	Negative	H. capsulatum	H. capsulatum
5	Contaminated	Negative	H. capsulatum	Negative
6	H. capsulatum	H. capsulatum	Negative	Contaminated
7	H. capsulatum	Contaminated	Negative	H. capsulatum
8	H. capsulatum	H. capsulatum	H. capsulatum	Negative
9	H. capsulatum	Negative	H. capsulatum	H. capsulatum
10	Negative	Negative	Negative	Negative

Mice Infected with B. Dermatitidis

Mouse No.	Mice Receiving Testosterone Compounds		Mice Receiving Control Vehicles	
	Total Mesentery, Including Infected Nodules	Liver	Total Mesentery, Including Infected Nodules	Liver
1	Negative*	Negative	B. dermatitidis	Negative
2	Negative	Negative*	Negative	B. dermatitidis
3	Negative*	Negative*	Not cultured	Negative
4	Negative	Negative	B. dermatitidis	B. dermatitidis
5	Negative*	Negative*	B. dermatitidis	Negative*
6	Negative*	Contaminated	Negative*	Negative
7	Negative*	Negative	Negative*	B. dermatitidis
8	Negative	B. dermatitidis	Negative	Negative
9	Negative*	Negative*	B. dermatitidis	Negative*
10	Negative	Negative*	B. dermatitidis	B. dermatitidis

* Heavy growth of yeast obtained from tissue. The species of yeast has not been determined beyond ascertaining that it is not Candida, and most probably is a member of the tribe Saccharomycetaceae. No attempt was made to demonstrate ascospores.

TABLE 5.—*Weights of Critical Tissues of Mice Experimentally Infected with B. Dermatitidis, H. Capsulatum, and C. Immitis*

	Mice Infected with B. Dermatitidis, Strain 7A2				
	No. of Mice	Mean Wt. of Mice, Gm.	S. D.	Mean Wt. of Mesentery, Including Infected Nodules, Mg.	S. D.
Mice receiving testosterone, aqueous suspension	5	27.76	±4.62	509.60	±123.77
Mice receiving testosterone propionate in oil	5	30.06	±4.34	488.04	±166.16
Mice receiving saline control	5	29.40	±1.86	792.02*	± 64.14
Mice receiving oil control	5	28.84	±2.15	561.46	± 53.94

	Mice Infected with H. Capsulatum, Strain 9A12						
	No. of Mice	Mean Wt. of Mice, Gm.	S. D.	Mean Wt. of Spleen, Mg.	S. D.	Mean Wt. of Liver, Mg.	S. D.
Mice receiving testosterone compounds	10	26.46	±3.92	374.25	±99.25	2,334.89	±396.25
Mice receiving control vehicles	10	28.91	±2.51	363.38	±36.89	2,308.86	±149.23

	Mice Infected with C. Immitis, Strain 11A2				
	No. of Mice	Mean Wt. of Mice, Gm.	S. D.	Mean Wt. of Infected Nodules in Peritoneal Cavity, Mg.	S. D.
Mice receiving testosterone compounds	10	±26.73	1.42	189.76	±293.14
Mice receiving control vehicles	10	±26.04	2.14	213.68	±272.47

	Uninfected Mice								
	No. of Mice	Mean Wt. of Mice, Gm.	S. D.	Mean Wt. of Mesentery, Mg.	S. D.	Mean Wt. of Spleen, Mg.	S. D.	Mean Wt. of Liver, Mg.	S. D.
Mice receiving testosterone aqueous suspension	5	28.46	±4.01	494.96	58.44	227.18	±97.64	1,898.46	±299.63
Mice receiving testosterone propionate in oil	5	28.30	±1.75	438.76	45.07				
Mice receiving saline control	5	27.00	±1.79	597.60	82.42	182.20	±22.89	1,992.31	±167.45
Mice receiving oil control	4	31.35	±2.12	685.75	75.13				

* Significant between 1% and 0.1% probability level, on assumption of conformity to a normal distribution.

TABLE 6.—*In Vitro Assay of Fungistatic Activity of Pooled Sera of Mice Receiving Testosterone Propionate in Oil Subcutaneously*

		Fungus Strain			
		H. Capsulatum		B. Dermatitidis	
	Dilution	7A2	7A9	9A12	9A14
Sera A, (mice receiving testosterone propionate)	1:10	++++	++++	++++	++++
	1:100	++++	++++	++++	++++
Sera B, (mice receiving corn oil control)	1:10	++++	++++	++++	++++
	1:100	++++	++++	++++	++++
Sera C, (mice receiving nothing)	1:10	++++	++++	++++	++++
	1:100	++++	++++	++++	++++
Testosterone propionate control	0.01%	0	0	0	0
	0.001%	++++	++++	++++	++++
Acetone control	0.4%	++++	++++	++++	++++
	0%	++++	++++	++++	++++

the ventral surface of the thorax was skinned, with the animal under ether anesthesia. From 0.2 to 1 cc. was obtained from each mouse. The collected bloods were refrigerated until clot retraction occurred. Cell-free serum obtained by centrifugation was diluted 1:10 and 1:100 with liquid medium containing 0.15% agar, modified after Salvin.[13]

The serum dilutions were distributed in sterile test tubes, 5 ml. per tube. Each tube was inoculated with 0.1 ml. of a 1:100 volumetric suspension of test fungus,[4] incubated at 37 C. and examined daily for growth. Serum collected from mice receiving 0.1 ml. of testosterone propionate in oil (Oreton, Schering), 50 mg. per cc. subcutaneously, daily for three days, failed to inhibit B. dermatitidis and H. capsulatum, in 1:10 dilution, as compared with sera from mice receiving 0.1 ml. of sterile corn oil daily for three days and mice receiving nothing, and with in vitro dilutions of testosterone, with acetone as the primary solvent (Table 6).

Reduction of Fungistatic Effect of Testosterone in Vitro in Presence of Plasma.—The addition of 1.0 ml. of citrated human plasma (blood bank discard) to pour plates prepared by the basic technique [4] resulted in a diminution of the fungistatic effect of testosterone (Table 7).

TABLE 7.—*Effect of Human Plasma on Fungistatic Activity of Testosterone in Vitro*

		Test Dilutions % Testosterone			Control Dilutions % Acetone	
% Plasma	Fungus Strain	0.01	0.001	0.0001	0.4	0
10	9A12	+	++++	++++	++++	++++
	9A14	+	++++	++++	++++	++++
	7A2	++++	++++	++++	++++	++++
	7A9	++	++++	++++	++++	++++
0	9A12	0	++	++++	++++	++++
	9A14	0	+++	X*	0	++++
	7A2	0	++++	++++	++++	++++
	7A9	0	++++	++++	++++	++++

* X = Contaminated.

CLINICAL INVESTIGATIONS IN TWO CASES OF HISTOPLASMOSIS AND ONE OF DISSEMINATED COCCIDIOIDOMYCOSIS

Reports of satisfactory treatment for histoplasmosis, both localized and disseminated, have been spasmodic. In all of the disseminated coccidioidomycosis infections in man it has been of no avail.

Curtis and Grekin [9] reported several cases of histoplasmosis in which the use of sulfonamides was effective.

Strong [13] reported a case of histoplasmosis with a solitary abscess which, after it was thoroughly curetted and dressed with antiseptic preparations (iodides?), remained healed for six months. The patient was not seen after that time.

Mantell and his associates § reported that their patient with histoplasmosis was asymptomatic for six months after a course of treatment with a pentavalent organic antimony preparation, namely, stibamine glucoside (Neostam).

Balina and his associates [14] had successful results in a patient who had ulcerations on the nasal septum caused by H. capsulatum and who was treated for nine months with sulfanilamide orally and sulfathiazole locally.

§ Cited by Melency.[15]

Meleney [15] treated a patient with histoplasmosis who had an ulcer on the tongue, with radium. The ulcer apparently healed nicely but recurred two years later.

Bismuth compounds and potassium iodide, thymol, quinine, penicillin, and other preparations have been used in histoplasmosis, without benefit.

REPORT OF CASES

Because of the fungistatic effect of the testosterone series in vitro, it was decided to test methyltestosterone in three cases of deep mycoses in male patients. Because of previous reports of the apparent disturbance of the immune mechanism and consequent bacterial infections associated with higher doses of the corticosteroids,|| and reports of the effectiveness of the sulfonamides in histoplasmosis [9] and other mycotic infections, we decided also to combine moderate amounts of meth-dia-mer-sulfonamides with high levels of methyltestosterone.

CASE 1.—*Extensive oral histoplasmosis.*

The patient was a white man, 45 years of age, who had had an oral infection involving the posterior left third of the tongue, the gingivae, and the larynx for two and a half years prior to being seen by us. Fifteen months earlier a diagnosis of widespread histoplasmosis had been made in Texas, based on biopsy and culture. X-ray films had revealed no lesions in the lung fields. Skin tests had not been done. Various medications used had failed to prevent extension of the disease. The patient had lost 35 lb. (15.9 kg.) in weight. He was then referred to the Vanderbilt University Hospital, Nashville, Tenn., where Dr. Amos Christie and Dr. Harrison J. Shull confirmed the diagnosis. Repeated skin tests of histoplasmin in strengths of 1:10 and 1:100 were negative, as were also repeated complement fixation studies for histoplasmosis. Over 200,000 mg. of oxytetracycline (Terramycin) was administered, without effect.

We first saw the patient on Feb. 25, 1952. He was emaciated and grossly ill. General physical examination revealed no other abnormalities. The disease seemed to be limited to the tongue, gingivae, and larynx.

Oral examination revealed extreme pyorrhea of the gingivae, with many carious teeth. There was a granulomatous lesion, 2 cm. in diameter, involving the posterior left third of the tongue. The lips appeared somewhat swollen. The uvula was swollen and somewhat more than normally firm, with a watery edema, but without definite infiltration. There were no infiltrations or lesions of the soft palate. There was a deep mass in the midportion of the tongue left of the midline. The epiglottis had been nearly destroyed, leaving a thickened base. The lingual mucosa was swollen and edematous. The upper edge and posterior surface of the epiglottis was replaced by a granular, ulcerated lesion, extending downward into the larynx to include the anterior half of the right aryepiglottic fold and the right false cord. There was some limitation of movement of the arytenoid because of general infiltration. The vocal cords were swollen and a little irregular but not ulcerated. The pyriform fossae appeared to be clear. Four pieces of tissue were removed, two from the laryngeal mass and two from the tongue. One piece from each site was placed in formalin solution for microscopic examination, and the other specimens were sent to us for bacteriologic and mycologic study.

The cultures were positive for H. capsulatum from both the gingival and the tongue lesions. The histoplasmin skin test, 1:1,000 dilution, was negative on March 2, 1952. The patient's complement fixation titer was not determined at the onset.

Microscopic Pathology.—Microscopic examination of the fixed tissues showed the upper portion of the epidermis to have a basket-weave appearance, varying from 3 to 5 cells in depth. In the remainder of the epidermis many squamous cells were without nuclei. There was an intense proliferation of the epithelium. On close examination the intercellular bridges were seen to be intact. There was mitosis of the cells throughout the epithelium. The basal layer retained its palisade arrangement. There was no invasion of the epidermis by the underlying

|| References 16 and 17.

infiltrate, but instead the epidermis tended to push aside the infiltrate in the corium. A second outstanding feature was the predominance of lymphocytes in the infiltrates and the presence of histiocytes, occasional plasma cells, and many Touton foreign body giant cells. In some areas these Touton cells contained 20 to 25 small organisms, 2 or 3μ in diameter, with a rather clear "capsule" (hematoxylin and eosin stain). They were thought to be the intracellular organisms seen in the tissue phase of H. capsulatum.

Table 8 shows the dosage and results of treatment.

On Feb. 25, 1952, he was given 300 r of x-ray therapy, using an oral cone, 0.5 half-value layer 0.7 mm. Cu, 200 kv. at 50 cm. distance to each side of the submaxillary region, 10 by 15 cm. field, which included the tongue and the larynx. He was given a total dose of 1,000 r

TABLE 8.—*Summary of Case Histories*

Case	Diagnosis	Culture and Biopsy	Skin Test	Complement Fixation Titer	Approximate Duration of Disease Before Testosterone-Sulfonamide Therapy	Duration of Testosterone-Sulfonamide Therapy
1	Histoplasmosis (extensive oral and laryngeal)	Culture +; organisms seen in tissue	Neg.	Not determined before therapy On 1/16/54 and 1/24/54 neg.	18 mo.	2 yr. (sulfonamides discontinued last 3 mo. of observation because of nausea)
2	Histoplasmosis (localized, oral)	Culture +; organisms seen in tissue	Pos.	Not determined before therapy On 2/4/54 neg.	14 days	6 mo. (64 days regular; last month of observation irregular)
3	Coccidioides (disseminated)	Culture +; organisms seen in tissue	Neg.	Titer fluctuated (see Table 10)	54 days	9 mo.

TABLE 9.—*Summary of Therapy Used*

	Methyl Testosterone			Meth-Dia-Mer Sulfonamides				
Case	Daily Dose, Mg.	Duration of Treatment	Total Dose, Gm.	Daily Dose	Duration of Treatment	Total Dose, Gm.	X-Ray	Result
1	50-100	2 yr.	36.5	3-6 tablets, 0.5 gm. each	1 yr. (took 1 mo., then discontinued 1 mo., etc.)	270	1,000 r to each submaxillary and cheek, cross-fired 20 ma., 200 kv., Thoraeus A filter, 50 cm. dist.	Disease apparently arrested 2 yr.; cultures negative Recurrence 3/15/54; biopsy positive
2	100	6 mo.	12.4	3-6 tablets, 0.5 gm.	3 mo.	135	1,800 r with oral cone, port 2 cm. in distance; same factors as above	Patient cured
3	100-250	9 mo.	54	3-6 tablets, 0.5 gm.	9 mo.	540	250 r to rt. cervical area, 175 r to left cervical, and 250 r to mediastinum; same factors as above	Infection arrested

to the right and left fields. At the same time he was given methyltestosterone, 50 mg. daily. He was also given meth-dia-mer-sulfonamides (Terfonyl), two tablets, 7.7 grains each, four times a day. On March 19, he became very hoarse, and the methyltestosterone was increased to 100 mg. a day. On April 5 he began to feel weak. The meth-dia-mer-sulfonamides were reduced to one tablet four times a day, and 2 cc. of crude liver extract was given intramuscularly twice a week. The methyltestosterone was continued. On Sept. 29, 1952, the patient was given an intradermal histoplasmin test, to which his reaction was slightly 1+ (positive). At the same time, a coccidioidin test proved to be negative. At this time his dentist began removal of about two teeth a week. His gums healed promptly after extraction of all the teeth. The high dose of the steroid was continued, but the sulfonamides were discontinued.

On Nov. 24, 1952, examination of the patient's gums showed them to be healing nicely. The histoplasmic pyorrhea had disappeared. There were no signs of infection on the tongue

or larynx. The active disease was apparently completely arrested. Smears from the gum and tongue revealed no growth of H. capsulatum. A biopsy was made. No encapsulated organisms were found.

In June, 1953, he developed a leucokeratotic area 1.8 cm. in diameter on the left gingiva. This area became infiltrated. A month later diagnosis of squamous cell carcinoma was made. Gamma radiation with low-intensity radium needles (8,000 gamma r) completely destroyed this growth.

On Feb. 15, 1954, the patient had gained 40 lb. (18 kg.) in weight and was in an excellent general condition. He had remained on 50 mg. of methyltestosterone a day for a year and had taken meth-dia-mer-sulfonamides intermittently. Examination of the larynx revealed only edema, possibly produced by scar tissue on the old ulcerated areas.

On March 15, 1954, the patient returned, complaining of repeated vomiting, soreness of the throat, and loss of 6 lb. (2.7 kg.) of weight in four weeks. A report from the otolaryngologist (Dr. L. C. McHenry) was as follows:

"His voice was husky and there was obvious air leakage. No remarkable swelling externally was seen, although there were a number of small, palpable glands along the carotid sheath. Patient had no lower alveolar ridge, and there was still some leucoplakia in this area. On mirror examination the epiglottis had healed. There was no swelling in area of the base where the lesion had been on the right side. The right aryepiglottic fold and arytenoid were swollen and red. An ulcerative lesion involved the right false cord and the right vocal cord. This extended around into the posterior commissure, where there was involvement and some piling up of tissue, which apparently also extended below the level of the vocal cords. The entire left side of the larynx seemed to be relatively fixed, although the vocal cord while edematous seemed to be intact. There was limitation in motion of the left side of the larynx."

Dr. McHenry's conclusions were that there was still an active process of some sort in the larynx. There had been healing of areas that were not healed two years ago, but there was also obvious extension downward which was not previously present.

Microscopic examination on April 10, 1954, showed one large fragment of squamous epithelium; within this fragment there were several small cystic spaces, which appeared to be degenerated and partially necrotic tissue. In this area there were groups of inflammatory cells, some of which were polymorphonuclear leucocytes. In the hematoxylin-and-eosin-stained section there was faint evidence of small organisms which had the appearance of being H. capsulatum. It was somewhat difficult to be absolutely certain with this stain that these were Histoplasma organisms; however, an additional section was prepared with Schiff's stain, and this stain revealed many organisms that appeared to be typical of H. capsulatum.

Microscopic diagnosis: Histoplasmosis of larynx.

The following additional laboratory tests were made:

Complement fixation for H. capsulatum. (Feb. 28, 1954): Negative.

Fluoroscopic examination after a barium meal (March 15, 1954): No strictures of the esophagus or any extension to this area.

Roentgenogram of the chest (March 23, 1954): Normal.

Sperm count (March 23, 1954): Volume, 1 cc.; viscosity, normal; turbidity, normal; color, opaque white; sperm count, 0 (aspermia).

Sulfobromophthalein (March 23, 1954): No dye retention at 45 minutes.

Cephalin flocculation: Negative in 24 hours.

Collection of a 24-hour specimen of urine (March 26, 1954): Creatine, 313 mg. per 24 hours, creatinine, 2,620 gm. per 24 hours (high creatinuria probably from high dosage of methyltestosterone).

CASE 2.—*Localized oral histoplasmosis.*

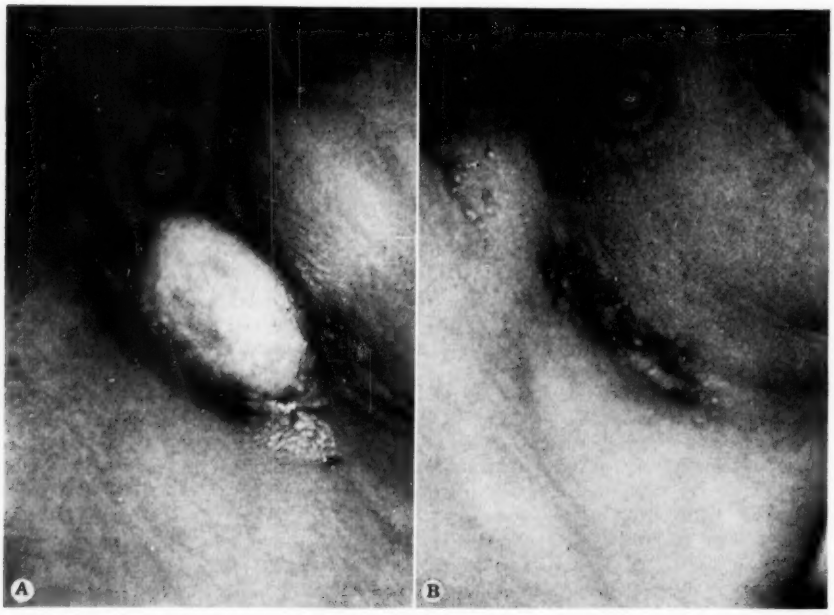
The patient, a white man, aged 24, noticed a small nodule on his tongue four days prior to his first office visit, on July 1, 1953. He stated that the lesion began as a very small nodule and gradually enlarged. The lesion was asymptomatic at the time of our first examination. It was 1 cm. in diameter, located in the middle of the tongue at the junction of the middle and distal thirds and was firm and painless. There were no other cutaneous or oral lesions. The patient's general physical condition was excellent. The lesion was diagnosed as a granuloma,

possibly histoplasmosis. A biopsy specimen was taken and cultures were made. Wassermann reaction of the blood was reported negative.

H. capsulatum was isolated from the lesion on Sabouraud's agar at room temperature. A skin test with 0.1 cc. of histoplasmin, 1:100, was 4+ (positive).

Examination of the tissue section revealed several large histiocytes which contained dark-staining organisms (hematoxylin and eosin stain) measuring 2 to 4 μ in diameter. The organisms were enclosed in a capsule. Diagnosis: Histoplasmosis.

The patient was treated (Table 4) with 100 mg. of methyltestosterone daily for 64 days. In addition three 7.7 grain tablets of meth-dia-mer-sulfonamides were given a day. X-ray therapy (1,800 r) was delivered with a 2 cm. oral cone to the area on the center of the tongue—200 r daily for nine days, half-value layer 1 mm. Cu, 50 cm. distance, Thoraeus A filter, 200 kv. The steroid and sulfonamide treatments were continued intermittently for six months.



Disseminated coccidioidomycosis (Case 3) showing results of methyltestosterone and meth-dia-mer-sulfonamide therapy. *A*, large granuloma of the right supraclavicular area; *B*, one year later.

but in the past six months all therapy has been discontinued. The lesion healed completely and remains well. The area of infection has shown an area resembling a transitory benign plaque with loss of papillae, but no sign of recurrence of the granuloma has been observed.

Sperm count (Feb. 12, 1954): volume, 3 cc.; color, opaque white; viscosity, increased; turbidity, normal; motility, 90%; 82,000,000 sperm per cubic centimeter.

CASE 3.—*Generalized coccidioidomycosis.*

A Negro, aged 29, reported to the University Hospital on March 3, 1953. Two weeks previously the patient had been perfectly well, before the onset of a large swelling on the right side of his neck. His temperature was 99 F., and for the last few days he had had a cough that produced yellowish sputum. The patient had worked each fall from September to December on a farm 22 miles east of Phoenix, Ariz.

Physical examination revealed a well-developed, thin, Negro, only slightly ill. He weighed 159 lb. (72 kg.). The lower cervical nodes were moderately enlarged, and one on the right side of the neck was fluctuant and measured 6 by 3 cm. There was a group of corymbose

papules on the left cheek and a deep pustule on the point of the chin. No other abnormalities were found. White and red blood cell counts were normal; total protein, 8.7 gm. per 100 cc. Albumin-globulin ratio, 4.7:4.0; Wassermann reaction of the blood, negative. A roentgenogram of the chest showed marked hilar shadows and enlarged nodes in the right hilus. When the large cervical node became fluctuant, the lesion was aspirated; cultures were made, and biopsy was performed (March 16, 1953).

On pathological examination the normal architecture of the node was found to have been obliterated. There was a slight fibrous proliferation. The pattern of cells consisted of pleomorphic lymphocytic plasma cells, a few typical reticulum cells, and a scattering of eosinophiles. There were no areas of necrosis or fibrosis. No Dorothy Reed cells, characteristic of Hodgkin's granuloma, were seen. The slide was considered to be consistent with Hodgkin's paragranuloma.

A diagnosis of Hodgkin's disease was made, and the patient was referred to the radiology department for treatment. On March 21, 1953, intermediate x-ray therapy (200 kv., 18 ma., Thoraeus A filter, HVL 1 mm. Cu, at 50 cm. distance) was begun. The patient was given 75 r to the right and left cervical nodes. (The total roentgen therapy consisted of 275 r to

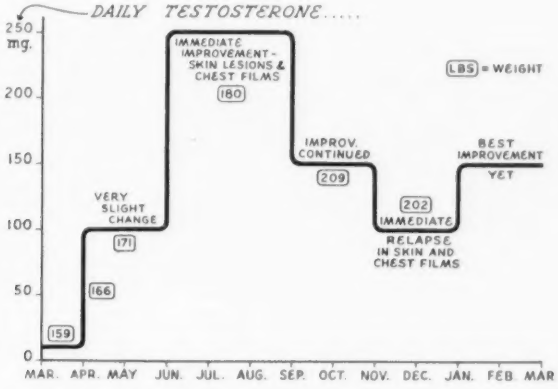


Chart showing course of disseminated coccidioidomycosis on methyl testosterone and meth-dia-mer-sulfonamides.

the mediastinum, 250 r to the right cervical nodes, and 175 r to the left cervical nodes.) Other cervical nodes began to enlarge in spite of this treatment. Treatment was discontinued on March 25, when cultures of several tubes of Sabouraud's agar revealed typical whitish-gray fungous colonies of C. immitis, and microscopic examination revealed the barrel-type arthrospores typical of this organism.

A biopsy of skin from the chin lesion was made. Many Langhan's giant cells (some 60 to 80 μ in diameter) were found containing typical "sporangia" of C. immitis. The lesion was diagnosed as coccidioidal granuloma of the skin.

On March 26, 1953, new lesions began to appear on the face and at the base of the left thumb. They were verrucous and discharged a purulent exudate. Complement fixation test for C. immitis, done on March 27, 1953, by Dr. C. E. Smith, Berkeley, Calif., was reported 4+ (positive) at 1:128 dilution, and 2+ (positive) at 1:256. Dr. Smith wrote: "This certainly is an interesting case, and we completely confirm the diagnosis of disseminated coccidioidal infection. Anergy is further evidence of poor prognosis." Skin tests with coccidioidin were negative on April 2 and April 9. The tentative diagnosis of Hodgkin's disease was changed to that of disseminated coccidioidomycosis of the lungs, skin, and lymph nodes, with a negative skin test and elevated complement fixation titer. These findings in a Negro presented an extremely grave prognosis.

On April 17, treatment was started with testosterone (10 mg. a day) and meth-dia-mer-sulfonamides, two 7.7 grain tablets t.i.d. (Chart). The patient remained at home at complete

bed rest. On May 15 he returned to the hospital. The disease had not progressed. At this time the daily dose of testosterone was increased to 100 mg. On April 16, 1953, a coccidioidin intradermal test was again performed. There was no reaction. From June 5 to June 26 he took 250 mg. of testosterone a day and continued taking meth-dia-mer-sulfonamides at the previous dosage. During this interval the disease definitely regressed. No new lesions appeared, and a roentgenogram of the chest revealed a decrease in the size of the hilar lymph nodes. From June 26 to Aug. 7 the dose of the methyl testosterone was reduced. The patient took 150 gm. a day and continued the same dosage of meth-dia-mer-sulfonamides.

By Sept. 30, 1953, all the lesions had healed except the original mass in the right cervical region. This lesion, formerly about 6 cm. in diameter and discharging a purulent exudate, was now about 3 cm. in diameter and without ulceration or exudation. Other nodes were very small or had disappeared. A roentgenogram of the chest showed a further decrease in the size of the hilar nodes. The patient had gained 36 lb. (16.3 kg.). On Dec. 15 the dose of testosterone was reduced to 100 mg. a day. In two weeks there was a noticeable softening and draining of previously healed nodes with enlargement of hilar infiltrations, as revealed by a roentgenogram of the chest. On resuming the 150 mg. dosage, the patient immediately began

TABLE 10.—*Complement Fixation Titer of Case 3 (Coccidioidomycosis) During Therapy with Methyltestosterone and Meth-Dia-Mer Sulfonamides*

	Dilution of Serum, per Cc.*						
Date	1:2	1:4	1:16	1:32	1:64	1:128	1:256
3/27/1953	++++	++++	++++	++++	++++	++++	++
	0.2	0.1	0.05	0.025	0.0125	0.006	0.0031	0.0015
9/ 1/1953	++++	++++	++++	++++	++++	±	0	0
11/17/1953	++++	++++	++++	++++	++++	++	0	0
2/15/1954	++++	++++	++++	++++	++++	++++	+++	0
3/10/1954	++++	++++	++++	++++	++++	+++	±	0
3/25/1954	++++	++++	++++	++++	++++	+++	±	0
8/25/1954†	++++	++++	++++	++	—	—	—	—

* Data for 3/27/1953 from Smith, Berkeley, Calif.; other data from Biddle, Los Angeles General Hospital.
† Every indication shows that the complement fixation test is becoming negative.

to improve again, and on Feb. 28, 1954, there was no further draining and all nodes had disappeared. He has gained 40 lb. (18 kg.) over his weight when first seen and shows no ill effects of the drug except a slight bilateral gynecomastia and moderate creatinuria. On March 5, 1954, the chest roentgenogram showed there was a slight regression in the size of the hilar shadows and lung fields were clear. [Repeated skin tests to coccidioidin 1:100 in July, August, and September, 1954, showed a mild erythema (1+ reaction).]

The following additional laboratory tests were made:

Liver function tests—Sulfobromophthalein, (July 16, 1953): 45 minutes, 19.9% dye retention; (March 7, 1954): 45 minutes, 8.1% dye retention; van den Bergh's bilirubin test, (March 7, 1954): Total, 2.0 mg. per 100 cc. Direct, 1.1 mg. per 100 cc. Indirect, 0.9 mg. per 100 cc.

Total protein: 8.0 gm. (albumin-globulin ratio, 5.2:2.8).

Prothrombin—whole plasma: 14.2 seconds.

Alkaline phosphate: 1.1 Bodansky units.

Blood creatine (April 16, 1954): 132 mg. per 24 hours; creatinine, 2.94 gm. per 24 hours.

Sperm count (March 16, 1954): Volume, 1 cc.; opaque white, normal viscosity and turbidity. No sperm were found. Diagnosis: Aspermia.

COMMENT

Previous attempts at therapy in histoplasmosis and coccidioidomycosis have been unsatisfactory. Use of steroid compounds and stilbene derivatives in coc-

cidioidomycosis has also been disappointing. Pregnenolone acetate in doses as high as 1 gm. daily and stilbamadine in coccidioidomycosis have failed to control this disease.¶

Because of its high concentration in reticuloendothelial tissues, Prior and his associates,[19] in an excellent study of histoplasmosis in Ohio, suggest quinacrine hydrochloride (Atabrine) 200 mg. t.i.d., in the treatment of histoplasmosis. These workers found quinacrine fungistatic against H. capsulatum in the test tube and were able to demonstrate an increase in survival of mice experimentally infected with this fungus. They state that all sulfonamides and antibiotics in general use have proved ineffective in the treatment of active histoplasmosis. They concluded that in the disseminated disease, as in tuberculosis, treatment is still supportive and that no specific drug is available for the acute fulminating form of the disease.

Methyltestosterone is a safe steroid and is especially suitable in histoplasmosis, since the majority of cases occur in males [18] after the age of 10 years.

Methyltestosterone is a chemical compound which can be given safely in large doses in the male without disastrous effects. No injurious effects to the nervous system are seen, as in therapy with the stilbene group. Methyltestosterone causes physiologic creatinuria and is contraindicated in diseases causing creatinuria, i. e., thyrotoxicosis, dermatomyositis and other muscle dystrophies, in which there is already a deranged protein metabolism. There may be a suppression of spermatogenesis, as was demonstrated in two of our cases in which large doses of testosterone were received over a long period of time.

Alamaden and Ross [19] reported a case of jaundice following the administration of small doses of methyltestosterone. This is the 19th case reported in the medical literature. Although a severe and progressive jaundice occurs, the usual laboratory tests for hepatocellular damage are negative. Complete recovery follows the discontinuance of methyltestosterone. This reaction was not seen in the three cases reported. The liver function tests in two cases showed no hepatic damage from testosterone in high, prolonged dosage. A mild creatinuria was noted in two cases only after long administration of the drug.

All have shown satisfactory, immediate improvement in doses above 100 mg. with methyltestosterone combined with sulfonamides.#

Case 1, of histoplasmosis, was a serious, extensive, hopeless one. The disease showed no signs of recurrence for one and a half years. The patient had taken 50 mg. of methyltestosterone and two 7.7 grain tablets of meth-dia-mer-sulfonamides for over a year. However, the dosage of the steroid was apparently maintained at a blood level below that which is fungistatic for H. capsulatum, since for the last month the patient has suffered from an extension of his disease. The dose has been increased to 200 mg. of methyltestosterone and 3 gm. of meth-dia-mer-sulfonamides each day, but it is too early to tell whether he will respond again to the medication.*

¶ Wilson, J. W.: Personal communication to the author.

Methyltestosterone has been furnished by the Schering Corporation.

* Since the formal reading of the paper, the patient under discussion has made a slow improvement, with a gain in weight and healing of the laryngeal process. His dosage of methyltestosterone has been maintained at 200 mg. a day.

Case 2, a case of localized histoplasmosis, made a quick recovery, and, although he has discontinued his treatment, the patient is entirely well.

Case 3, of disseminated coccidioidomycosis in a male Negro, had a very grave prognosis, with involvement of lungs, skin, and lymphatics. The complement fixation test early in this case was strongly positive, and the skin test has been repeatedly negative, showing a marked anergy to the infection, with a poor prognosis.

The patient has gained 40 lb. (18 kg.) in weight and is in good health, but with only slight improvement in his complement fixation test. His skin test shows 1+ reaction to coccidioidin 1:100. His disease can be considered arrested.

These cases have been reported to give encouragement to others who have to care for these heretofore hopeless types of deep mycoses. Two of the fatal disseminated cases of histoplasmosis in the male reported by Prior and his associates [18] would have been excellent subjects for this combined type of therapy.

In the disseminated deep mycosis it is suggested from the experiences in our two cases that a certain level of testosterone must be maintained, i. e., at least above 100 mg. a day, combined with a moderate dose of meth-dia-mer-sulfonamides. The ability of the immune mechanisms of the body to create a permanent immunity to these encapsulated and spore-forming deep fungi without the aid of the steroid is improbable. The slow improvement in complement fixation titer in the patient with disseminated coccidioidomycosis (Case 3), although by all clinical signs the disease is arrested, substantiates this hypothesis.

It is hoped that further clinical trial will show this combination of therapy to be as efficacious as here reported, but time and numerous cases will prove or disprove its value. Complete cure cannot be claimed in these diseases by any of the stilbene or steroid compounds. The time elapsed has been too short. The relapse in the fulminating case of histoplasmosis after two years' apparent arrest was disappointing (Case 1).

The steroids when used as antimycotic agents may have a refractory period, as has been reported in laboratory experiments on the effect of hormones on general metabolism in animals. After a time there is a diminution of the usual action of testosterone on nitrogen retention, water balance, and Na and K levels. Also, in dermatomyositis the clinical response to testosterone reaches a certain refractory period when further trial seems ineffectual. The ability to retain exogenous creatine (creatine tolerance test), the myotrophic effects, and the apparent anabolic effects become greatly diminished.

Clinical trial seems to be the best method of testing the steroid products in human fungous infections. In vitro studies with these compounds cannot always be relied upon to demonstrate which have the best antifungal properties in human infections.

SUMMARY

Three cases of deep mycoses have been treated with a combined therapy of methyltestosterone and sulfonamides (meth-dia-mer-sulfonamides).

This combined therapy produced apparent arrests in one case of histoplasmosis and one case of disseminated coccidioidomycosis. The third case (histoplasmosis) has suffered a recurrence after one and one-half years' arrest of the disease.

All the testosterone series, including testosterone, methyltestosterone, and testosterone propionate, showed good inhibition of Histoplasma capsulatum and moderate inhibition of Coccidioides immitis by in vitro studies.

No reactions of serious nature were encountered in prolonged use of methyltestosterone. Moderate creatinuria was noted in two cases and slight gynecomastia in one.

ABSTRACT OF DISCUSSION

Dr. M. F. Engman Jr., St. Louis: A paper such as this by Dr. Lamb and his associates, in which are reported both therapeutic results with patients and carefully controlled laboratory experiments, seems to me to be far more interesting and instructive than separate papers, each dealing with one phase of the same problem. This is a brilliant therapeutic triumph, even though in one case of histoplasmosis there has been a recurrence. As a matter of fact, the recurrence emphasizes the previous effectiveness of the therapeutic agent. This paper is of particular importance because it reports the first successful use of methyltestosterone as a chemotherapeutic agent in histoplasmosis and coccidioidomycosis.

Local and systemic infections with these fungi are not at all rare, especially in subclinical form, if we are to accept the positive histoplasmin and coccidioidin skin tests as evidence of previous or present mild infection. Furcolow and others have reported many interesting studies which imply that an enormous percentage of the population in the Middle West have a mild histoplasmosis, usually early in life. In the desert states, mild coccidioidomycosis, or "San Joaquin fever," is a most prevalent disease, at least on the evidence of positive skin tests with coccidioidin. Furcolow and some others have reported their observations on workers in mycological laboratories. Skin reactions to histoplasmin would become positive, and at the time of this conversion a definite influenza-like illness occurred in some cases.

Apparently, then, the population in general possesses some sort of hereditary natural immunity or resistance to the fungi under discussion, as it does to a number of other diseases, such as syphilis and tuberculosis. The white temperate climate races seem to have a greater immunity than do the dark, jungle races. Acute fulminating cases, such as are here reported, are relatively rare.

Dr. Charles Dennie, in his book "The Gift of Columbus," offers a most interesting idea. He remarks that the white races through the centuries have gained an immunity to syphilis, but that "occasionally among a modern and civilized people there will be some individual who will have a throwback of this strange and awful disease as it was when it first appeared among mankind. It is my belief that his whole family, back to the original members, bore no immunity to the disease and that up to this time there had not been a single individual of that family who had ever contracted the disease; consequently, he had no natural immunity."

The cases here reported by Dr. Lamb and his collaborators may represent persons who for one reason or another have little or no natural immunity. Histoplasmosis and coccidioidomycosis may be old infections from the racial standpoint, or they may be present-day local representatives of related pathogenic fungi that have affected the white races for many hundreds of years.

Dr. John Eric Dalton, Indianapolis: The authors are to be congratulated on the fine therapeutic results which they obtained with a combined methyltestosterone-sulfonamide therapy in one of two cases of severe localized histoplasmosis and in another case of generalized coccidioidomycosis. Also, they are to be commended for the thorough laboratory and clinical studies which led them to introduce this treatment. Fortunately, they were schooled sufficiently to bypass the failures in their animal experiments and to carry their study directly to the infected human.

My experience with histoplasmosis and coccidioidomycosis is limited, and this is particularly true of the latter entity.

Histoplasmosis is endemic in Indiana, and the Pediatric Service of Indiana University Medical Center has been interested particularly in the manifestations of this disease in infants and young children. In that age group they have seen some 10 cases, occurring in both sexes. Some of these patients were treated by the earlier suggested vanillate therapy, but, like others, the interest of these workers in that treatment is decreasing because of its inconstant effect and its hazards of administration.

The diagnosis and prognosis of these two diseases is often perplexing, because both may show clinical or subclinical forms, both may be localized or generalized in nature, both or the same type of either may differ greatly in its severity, both may fulminate and terminate rather rapidly in death, and both may go to a slow spontaneous cure. For these reasons and because of the scarcity of such cases, it is difficult for individual workers to evaluate a treatment program directed against these diseases. Therefore, the presenters ask that others check these results and thus aid in establishing the merits of this treatment.

It is inconceivable that the first case of localized histoplasmosis or the one of generalized coccidioidomycosis had any spontaneous cure element in their arrest. Furthermore, it would seem amiss to practice therapeutic nihilism while awaiting a spontaneous cure in a disease which can also fulminate. However, since remissions are reported in cases of localized histoplasmosis treated by radium, one asks whether the roentgen therapy used in Cases 1 and 2 could have contributed in any part to their cure.

Because Cases 1 and 3 showed aspermia, following the prolonged use of large doses of methyltestosterone, it becomes necessary to know whether that finding is always reversible. Unless a normal spermatogenesis would be resumed constantly on the reduction of the dose, or the discontinuance of this therapy, one would seriously weigh the initiation of this treatment in the young male adult, and then only if the patient agrees to this consequence.

The question whether the new area of histoplasmosis in Case 1 arose because of the patient's becoming refractory to this therapy, or whether it occurred because of the reduced antifungal blood levels resulting from the decreased doses of methyltestosterone, will probably be answered in the further follow-up of this patient. If he again responds to elevated doses of this hormonal steroid, we may again be confronted with the possible problems arising from a maintained continuance of the high doses of this substance.

Furthermore, these diseases occur also in young children and women, in whom the administration of methyltestosterone would be contraindicated. However, there may be another substance less active androgenically than methyltestosterone, but equally effective fungistatically —such as progesterone—and it could possibly be combined with the sulfonamides in the treatment of histoplasmosis in the female and the child.

This paper continues that constant and commendable search for those ideal fungistatic agents which are of high potency, both topically and orally or parenterally. Such studies grew from an original postulation regarding the possible relationship of steroid hormones in immunity. Thus, various hormonal steroids were investigated for their antimicrobial activity, and these studies were later expanded to include the amino and other nonhormonal steroids, aromatic diamidines, stilbenes, and still other agents. From that accumulated work, the opinion is now accepted, generally, but possibly not fully, that the therapeutic action of all these effective agents depends upon their true antimicrobial action, rather than upon their hormonal effect. Furthermore, it now seems clear that no single agent will be found which will be effective against all strains of fungi or the variants within these individual groups.

Dr. J. Walter Wilson, Los Angeles: This study reveals a good illustration of the fact that chemotherapeutic activity in vivo cannot be predicted by in vitro studies. These patients were benefited by amounts of drugs far below the dose needed to produce the same concentration in the body as that shown to be fungistatic in vitro.

Contrary to all experience in tuberculosis, we believe that in coccidioidomycosis there are two very valuable indicators of prognosis obtainable through the use of coccidioidin. Skin test reactivity, quantitated by using various dilutions of the material, can be used by the clinician as a measure of the resistance which the patient has mobilized against the progress of the disease at that time. The titer of the complement fixation test, again quantitated as in the Kolmer modification of the Wassermann test, can be used to estimate the amount of the disease the patient is fighting at a particular time. There is considerable evidence to show that in coccidioidomycosis the clinician may more reliably depend upon these two tests to predict the outcome in any particular patient than upon any other combination of laboratory or physical examination of clinical signs.

These same views seem to be valid in other deep mycoses, particularly blastomycosis of the North American variety and histoplasmosis.

Now, before you condemn these observations, please recall that all experience with intracutaneous testing with tuberculin is done with the protein, whereas coccidioidin is a true poly-

saccharide; also, that almost all our experience with complement fixation titers is derived from experience with syphilis, in which the antigen is a lipid, again in sharp contrast to coccidioidomycosis, in which this reaction takes place with a pure polysaccharide.

Much as I should like to see Dr. Lamb credited with discovering a miraculous cure, I shall withhold my judgment, with his permission, until the Coccidioides patient shows a skin test reactivity and a much more marked lowering of the complement fixation titer. I also consider it important that the case of histoplasmosis, on which improvement was really maintained, was one in which the skin test was positive, thus indicating that the patient had a high degree of immunologic resistance against the disorder.

Dr. Arthur C. Curtis, Ann Arbor, Mich.: I enjoyed this paper of Dr. Lamb's immensely. Our own in vitro experiments with the hormones showed, as did Dr. Lamb's, that methyltestosterone is by far the most fungistatic of the entire group.

I should also like to call Dr. Lamb's attention to an article by Curtis and Grekin[10] which was presented before the American Medical Association several years ago, on the cutaneous manifestations of histoplasmosis. In that article were described two patients, one with histoplasmosis of the tongue, the other with histoplasmosis of the penis and the satellite glands, in which sulfonamides were given. These patients were kept on those drugs for a period of almost a year, and in both instances biopsies showed a diminishing amount of the organism and eventually a complete clearance of the infection. One of the patients, a Negro who had histoplasmosis of the penis, came into the venereal disease clinic because he had this lesion on the genitalia. He had had several courses of penicillin, in spite of the fact that his serological tests had always been negative. Eventually, a biopsy specimen was taken, both of the penile region and of the gland, and the organisms were found. He was circumcised and put on the sulfonamides, and the lesions began to heal. We later saw him with a primary lesion of syphilis, for which we treated the patient. He came back, still later, with chancroid, and again was treated. Within the last year, he developed a squamous cell carcinoma of the penis, and has now had an amputation. In each case, we have had opportunities to do biopsies of the genitalia, and in each instance he has been entirely free of the organism.

Dr. John H. Lamb, Oklahoma City: I want to thank all of the discussers.

In answer to Dr. Dalton, progesterone can be used in place of testosterone, particularly 17-alpha-hydroxyprogesterone for females. The in vitro effect is almost as effective against these deep fungi as that of testosterone. In children, I suggest that pregnenolone acetate, 200 to 300 mg. daily, would be safe, since it has a moderate antifungal action against H. capsulatum. The cost of methyltestosterone, as you know, is becoming lower, as the sales have increased. It is now a very cheap hormone—$150 at wholesale prices is the approximate cost for a whole year's treatment for one patient.

Dr. Dalton also talked about the danger of aspermia. I believe these two cases were in a severe enough condition that it didn't make too much difference if the only reaction was the loss of their sperm. The Negro boy has two children and Case 3 is a grandfather. It is believed that the damage to the testes is not of a permanent nature on withdrawal of the hormone.

Dr. Wilson is right in his doubting a cure, and we are dubious, too. We think these cases are not cured at all, at least 1 and 3. We think they are arrested, but time will tell whether there is a refractory period when large doses of the steroid fail to inhibit these two organisms.

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EFFICACY OF RESERPINE (SERPASIL) IN DERMATOLOGICAL THERAPY

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RESERPINE (Serpasil) represents a pure crystalline alkaloid of Rauwolfia serpentina, a small shrub indigenous to India. The roots of this plant had been used medicinally in Europe over 300 years ago for the treatment of anxiety states.[1] In 1933, its value as a hypotensive agent was reported by a group of Indian investigators.[2] Reserpine, thought to be the most important of the serpentine alkaloids, was first isolated in 1952 in Switzerland. Among the pharmacological effects noted was a quietude and reduction of emotional response.[3] At a conference on resperine and other alkaloids of Rauwolfia serpentina presented by the New York Academy of Sciences on Feb. 5, 1954, many aspects of the clinical value of this drug were discussed. In addition to its value as an antihypertensive agent, Wilkens [4] reported on the increased sense of well-being produced and on the ability of the drug to decrease neurotic symptoms in patients. Hafkenschiel and Sellers,[5] in discussing the value of reserpine as an antihypertensive drug, also remarked on the side-effects of relaxation and sedation. Reserpine apparently does not have the marked soporific and narcotic effects of the barbiturates. According to Wilkens,[4] "Patients tell you that Rauwolfia or reserpine will make them sleepy but will not put them to sleep." Harris,[6] in discussing the use of reserpine in geriatric hypertensives, also commented on the relaxing qualities of this drug. Kline,[7] in his discussion of the sedative qualities of Rauwolfia in neuropsychiatric patients, suggested that this drug be tried in other disorders, among which he included alcoholism, gastric ulcer, and atopic dermatitis. The tranquilizing qualities of reserpine in a number of patients with premenstrual tension have been described by Greenblatt.[8]

In considering the pharmacological action [3] of reserpine, it was noted that the major effect was the production of relaxation and sedation in the unanesthetized animal. It was also noted that the electroencephalogram showed a normal pattern in contrast to the sleep pattern seen with the use of barbiturates. Consequently, we felt that, in contrast to the barbiturates, the main action of reserpine, rather than a direct hypnotic action, is a tranquilizing one, which may permit but does not cause sleep.

When reserpine was administered to a dog, miosis, bradycardia, relaxation of the nicitating membrane, and augmentation of secretory and motor activity in the

gastrointestinal tract were among other responses noted. Reserpine also caused a slowly developing drop in the mean arterial blood pressure.

The exact mechanism of reserpine is not quite clear, but it is felt on the basis of the pharmacological observations that this drug acts on the central nervous system in the area of the hypothalmus. There appears to be an alteration of the sympathetic-parasympathetic balance by partial suppression of the sympathetic predominance. This might well fit in with the observation of Hess,[9] who feels that sleep is a parasympathetic function caused by suspension of sympathetic activity in the hypothalamus. Therefore, reserpine, which probably also causes some suppression of the sympathetic activity in the hypothalamus, might easily be expected to produce relaxation and tranquilization.

Additional studies dealing with the mechanism of reserpine have been carried out by Himwich and Rinaldi,* who have reported as follows:

In rabbits tested in a special experimental setup providing recordings of electrical potential changes from the brain cortex and from the reticular formation in the brain stem, Serpasil consistently was found to stimulate the reticular formation while its action on other areas was inconsistent. Since the reticular formation is known to be directly involved in arousal and sleep phenomena, the action noted above helps to account for the fact that Serpasil does not produce sleep even though it has a tranquilizing or sedative action.

In studying the effects of Serpasil on behavior and autonomic regulating mechanisms in the monkey, Schneider and Earl[10] summarized their findings as follows:

1. Reserpine (Serpasil) was given to a group of Macaca mulatta monkeys in varying doses and by different routes of administration. The effect on behavior, electroencephalograms, body temperature, systolic blood pressure, heart rate, respiratory rate, and pupillary diameter were studied.

2. Single i.v. doses of 0.5—1 mg./kg. and single oral doses of 50 mg. per kg. produce a state of quietude and unresponsiveness to extraneous stimuli, characterized by an essentially normal electroencephalogram, which distinguishes this state of tranquilization clearly from sleep induced by barbiturates.

3. Parallel to the changes in behavior, a drop in body temperature, an equivocal drop of blood pressure, a reduction of heart rate and respiratory rate were observed, whereas, miosis and diarrhea, commonly seen in other species after Serpasil were not present.

4. The threshold dose for chronic daily oral administration in the monkeys was 2—3 mg./kg.

5. Increasing the dose by all routes of administration did not enhance the effects observed but tended to prolong them. Toxic manifestations were not encountered after Serpasil in doses up to 4 mg./kg. i.v. and 400 mg./kg. orally.

6. The results of this study are in agreement with the experimental findings in other species and in man and further support the theory that the main point of attack of this drug is probably in the brain stem.

The following study was undertaken to evaluate the tranquilizing and relaxing effects of Serpasil † in a selected group of patients with dermatoses in whom a psychogenic factor was thought to be involved. There have been numerous reports attesting to the ability of this drug to alleviate free-floating anxieties without the concomitant soporific and sedative effects usually observed with the barbiturates.

* Himwich, H. E., and Rinaldi, F.: Personal communication to the authors.

† Provided by the Research Department, Ciba Pharmaceutical Products, Inc., Summit, N. J.

A series of 60 patients with various pruritic dermatoses, in whom for the most part a tension factor contributed to the cutaneous disorder, were selected for this clinical evaluation as follows:

Diagnosis	*No. of Patients*
Atopic dermatitis	19
Neurodermatitis (lichen simplex chronicus)	18
Nummular eczema	4
Infectious eczematoid dermatitis	2
Lichen planus	4
Pruritus ani	5
Dermatitis Herpetiformis	1
Pruritus vulvae	2
Neurotic excoriations	1
Seborrheic dermatitis	2
Chronic urticaria	1
Rosacea	1
Total	60

The dosage was 0.25 mg. four times daily for one month. Patients were reexamined at weekly intervals and questioned as to subjective sensations. Blood pressure and pulse were recorded each time. It was felt that in evaluating such a highly suggestible group of patients, some irrelevant questions concerning the drug, such as symptoms relative to joint pains, blurring vision, and the like, should be inserted among the routine questions in order that the study be as objective as possible.

In addition, 30 of these patients were arbitrarily maintained a month longer on placebo therapy without being notified of a change of medication, so that even further control could be exercised.

In analyzing the results, it was noted that most patients experienced moderate drowsiness and fatigue, starting usually from the second to the fourth day after onset of therapy and gradually subsiding during the second week. In general, there appeared to be a considerable variation in response to dosage; while it was felt that the clinical response to reserpine could be altered by varying the dose, a constant dosage was maintained for simplicity and standardization of this study.

Forty of the 60 patients experienced definite relaxation, tranquilization, sedation, and lessening of inner tension. There was no significant blood pressure or pulse change in this essentially normotensive group of patients.

Five additional patients with marked palmar hyperhidrosis were placed on reserpine therapy, 0.25 mg. four times a day. Within two weeks there was a decided reduction in the degree of hyperhidrosis. It was of special interest that these patients had failed to respond to previous local and oral therapy, including diphenmethanil methyl sulfate (Prantal) and methantheline bromide (Banthine). It is reasonable to suppose that reserpine would be of benefit in palmar hyperhidrosis since this condition is frequently associated with emotional factors, and further studies are in progress in order to evaluate this effect of reserpine.

Side-reactions, none of which was considered of major importance, were encountered as follows:

Nasal Congestion	24
Increased Appetite	13
Dreams	8
Nocturia	8

Therapy was discontinued in five patients during the first week because of marked fatigue, drowsiness, and weakness; in two patients with an asthmatic background because of moderate dyspnea; in two patients who developed nausea, and in one patient because of a moderate depression. All of these side-effects disappeared a short time after cessation of therapy. These patients are not included in the total of 60 evaluated.

Nasal congestion, representing the highest incidence of side-effects, for the most part appeared to subside with time. Many patients with increased appetites noted a corresponding weight gain. An interesting side-effect was nocturia where it previously had not existed. This fact might possibly be explained by an increased appetite and, therefore, corresponding increased fluid intake.

Of the 30 patients who were placed on the placebo therapy (after one month on reserpine), 22 stated that there was diminution in the degree of relaxation or sedation. Also, those patients with side-effects while on the active preparation noted that they disappeared soon after placebo therapy was instituted. The same objective type of interrogation as with the active drug was used. Many patients initially volunteered that they felt the pills had lost their effect. One patient, however, stated that he discontinued taking the tablets after two weeks of placebo therapy because of marked fatigue and nasal congestion, which occurred initially with the administration of the active drug, while, in general, it was noted that the effects of reserpine wore off by the end of two weeks. After it had been discontinued, in seven patients there appeared to be a reserpine effect extending beyond two weeks of placebo therapy.

SUMMARY AND CONCLUSION

Sixty patients with various dermatoses in which a psychogenic factor was thought to be a contributing factor, were placed on reserpine (Serpasil) for one month. Each patient took 1 mg. daily in divided doses. Thirty of these patients were further maintained for an additional month on placebo therapy. Patients were reexamined at weekly intervals, with blood pressure and pulse also being recorded.

Forty of the 60 patients experienced definite relaxation and tranquilization, and slept better.

Side-effects included nasal congestion, increased appetite, depression, dreams, nocturia, dyspnea, weakness, and nausea. These side-effects necessitated discontinuation of therapy in 10 patients, who are not included in the total of 60 evaluated.

Of the 30 patients maintained on placebo therapy, in 22 it was readily discernible that there was a diminution in the degree of relaxation or sedation and a lessening of the side-effects.

There was no significant blood pressure or pulse change noted in this essentially normotensive group.

Five patients with hyperhidrosis experienced moderate improvement while taking reserpine.

It is felt that the tranquilizing qualities of reserpine demonstrated in these patients with dermatoses affected by a psychogenic or emotional tension factor offer another tool to be added to the armamentarium of the dermatologist.

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GENITAL MONILIASIS AS A CONJUGAL INFECTON

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UNTIL recent years, moniliasis of the genitalia was regarded largely as a complication of diabetes or of pregnancy. In these instances, moniliasis has been familiar as vulvovaginitis in women, and, in the case of diabetic men, usually as intertriginous dermatitis of the genitocrural folds and surrounding areas. At times, also, in male diabetics, balanoposthitis has been encountered, attributable properly to invasion by Candida albicans as a result of circumstances in the skin and urine which enhance the growth of the yeast-like pathogen.

The introduction of broad-spectrum antibiotics heralded an upsurge in reports of monilial infections. Increasingly among nondiabetic and nonpregnant patients, it was asserted, monilial infection manifested itself in mucocutaneous and systemic forms. The ascendency of C. albicans was accounted for by the cataclysmic upset in biologic balance of the micro-organismal flora of the body and the suppression of antagonistic bacterial species, leaving the yeast-like forms to flourish rampant. As a consequence of the relatively unrestrained growth of C. albicans, characteristic clinical alterations might be produced, conspicuous among these being lesions in the buccal cavity and the genitoanal area.

Recently there has been a trend to deny this presumed increase of monilial infection caused by antibiotics. It has been the testimony of some authors * that little or no increment in mycotic infections has in fact taken place. The indictment of antibiotic therapy as the cause of moniliasis is ascribed by these authors to an erroneous clinical assumption that the finding of Candida in elevated numbers is tantamount to the demonstration of disease caused by these organisms. Their criticism is certainly valid if the finding of Candida is unsupported by clearcut and characteristic evidence of skin and mucous membrane lesions of moniliasis.

My experience, however, parallels that of reporters who have indicated awareness of a distinct and unequivocal increase in monilial eruptions as a complication of treatment with the broad-spectrum antibiotics chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin, Tetracyn), and chloramphenicol (Chloromycetin). Many confirmatory observations have been communicated to me also in an informal survey among a number of reputable dermatologists and gynecologists. While it would be unfeasible to authenticate this total experience (pro and con) statistically, the fact remains that there is a firm conviction among many competent clinicians that moniliasis is considerably more prevalent today, as a direct consequence of systemic antibiotic medication, than it was prior to the era of the antibiotic drugs.

During the past five years, concomitantly with increased recognition of cases of genital moniliasis among women, there has been in my practice a mounting inci-

* References 1, 2, and 3.

dence of cases of monilial infection of the external genitalia among men. I have observed nine male patients with genital pruritus and dermatitis, finding in each instance that the wife had a vaginal discharge or vulvar pruritus and dermatitis caused by C. albicans. (A curious sidelight on the distribution of cases is that four of the patients were physicians.) In four cases, the wife was pregnant, and in five cases the wife had received treatment with chlortetracycline or oxytetracycline shortly prior to the evolution of the husband's genital dermatitis. All of my male patients were in the 20- to 40-year age group and enjoyed excellent general health. I have not seen the eruption in men as a result of casual and nonmarital sexual exposure. Nor have I encountered examples, which I dare say occur, of sexual transfer of moniliasis from infected men to healthy women.†

CLINICAL MANIFESTATIONS

Moniliasis in Female Patients.—Monilial vulvovaginitis evokes the predominant complaint of pruritus of the vulva and adjacent areas, at times severe and of a burning character. Dysuria and dyspareunia are common. Examination discloses inflammation of the vaginal wall, and erythema and perhaps edema of the vulva. Often the vulvar eruption is pathognomonic, appearing as a macerated bright red dermatitis, the periphery of which may be studded with small, thin-roofed, and flaccid satellite vesicopustules or miliary erosions. The perineum and perianal area are nearly always involved. The dermatitis may extend over the inguinal folds, the crural areas, and the mons pubis. Visible at the introitus is a vaginal discharge, whitish or yellowish, not especially abundant, thin rather than thick (likened to watered-down buttermilk), and unassociated with distinctive odor. Often, but by no means always, cheesy flakes are present in the secretion or are found clinging to the vulva or vagina; these particles provide an excellent source for demonstration microscopically of fungous elements.

Variations of the foregoing description are common. Sometimes only mild pruritus is noted or none at all, together with little vulvar erythema and but slight discharge. These cases may not be recognized, because the patient may not complain, either for reasons of modesty or owing to a high threshold of sensation. In other instances, pyogenic infection complicates the disease, leading to painful follicular pustules and inguinal lymphadenitis. Distant portions of the body may be invaded by Candida, so that inframammary or axillary dermatitis may be produced, or perlèche, or stomatitis and glossitis, or paronychia of one or more fingers. When the primary infection is marked, sensitization eruptions of the skin elsewhere (moniliids) may make their appearance.

One more feature deserves comment. The vaginal disease is a notoriously recurring one, and recurring vulvar pruritus gives urgent notice of return of the vaginal infection. Once the fungus has gained ascendancy, it is subdued permanently with some difficulty. Contamination from skin, mouth, and intestinal tract are the conventionally incriminated routes of reinfection. It is barely possible that heightened virulence of the fungus accounts for the tendency to reinfect. It is more likely, how-

† After this paper was submitted for publication, I had the opportunity to study a married couple with genital moniliasis. The husband had developed a perianal dermatitis following treatment with oxytetracycline for a respiratory infection, and the eruption rapidly spread anteriorly to the genitalia. Several days later acute vulvovaginitis appeared in the wife. C. albicans was present profusely in both.

ever, that alterations in tissue resistance, both initially and as an aftermath of the inflammation, render skin and mucous membranes susceptible to subsequent and repeated invasion.

Moniliasis in Male Patients.—Among men moniliasis is represented as balanitis, balanoposthitis, crural intertrigo, or a diffuse eruption affecting the external genitalia and the perineal and anal areas. The eruption may seem insignificant, appearing only as a trivial erythema in the region of the corona of the glans penis, but not so the itching, which is usually severe. (In addition to the cases herein reported I have observed several cases of pruritus of the glans penis without eruption in which the development simultaneously with vaginitis in the spouse provided a clue to the diagnosis. Probably contact with irritating secretions rather than actual infection accounts for such a picture.) At the other extreme, the retrocoronal dermatitis may be sufficiently intense to lead to deep and raw erosions, painful fissures, and edema. Previous circumcision provides no safeguard against infection.

The scrotum is involved primarily or exclusively in some cases. This delimitation prevails among men using condoms in whom vaginal secretions directly infect only the scrotal skin. There seems also to be a greater tendency for infection of the scrotum and exclusion of the penis from infection among men whose hasty cleansing measures after coitus included the penis but neglected the scrotum. Several patients volunteered the information that prompt and careful postcoital bathing of the genitalia constitutes an adequate prophylactic measure.

Often only intertriginous dermatitis is visible in the genitocrural folds as a pruritic or painful eruption with or without maceration, encircled by tell-tale flaccid pustules and punctate erosions. At times the appearance is that of ordinary intertrigo, yet microscopic examination and culture of epithelial scrapings reveal C. albicans in abundance. Staphylococcal folliculitis may be superimposed as a painful complication, accompanied by lymphadenitis of the inguinal lymph nodes.

TREATMENT

The treatment of mucocutaneous moniliasis demands as a preliminary routine that predisposing systemic abnormalities, among which diabetes is preeminent, be sought out and corrected. A case that resists treatment requires sugar tolerance studies. Empirically, carbohydrates in the diet are restricted.

For local treatment of mycotic vaginitis a variety of agents is recommended. To be effective, treatment must be applied over a long period of time, in the light of the proclivity to recurrence. Common antifungal agents for vaginal use are 1% solution of methylrosaniline chloride (gentian violet) or methylrosaniline chloride suppositories, 1 to 4 strong iodine (Lugol's) solution U. S. P., 1:200 sodium borate (borax) douches, and proprietary preparations of fatty acids (caprylic, propionic, and undecylinic) and their salts.

In the treatment of vulvar and crural moniliasis in women, for several years I have found invaluable the suggestion of Dr. Oren A. Ellingson ‡ that a vaginal tampon be worn to minimize reinfection of skin by the vaginal discharge. This measure alone may suffice to promote healing of mild eruptions and will often lead to immediate improvement of severe eruptions. When local treatment is then applied, the skin in many cases responds favorably and with promptness that is impressive.

‡ Personal communication to the author.

The choice of any particular antifungal medication for the skin is not as important as the requirement that the medication be unirritating. I prefer to use weak solutions of salicylic acid (1 to 3%) in diluted alcohol, or resorcinol in 3 to 5% aqueous solution, or diluted Castellani's solution. Half-strength (2.5%) ointment of ammoniated mercury, or half-strength benzoic and salicylic acid (Whitfield's) ointment, N. F., or ointment of one of the fatty acids may prove adequate to cope with the infection. The fungous organism can be eradicated in most cases if predisposing causes are controlled and if reinfection is avoided.

When acute vulvar or scrotal, perianal, and crural dermatitis coexists with painful denuded areas, nothing is so rapidly effective as intermittent compresses of solution of silver nitrate, 1 to 1,000 to 1 to 500, in distilled water. Almost as satisfactory are intermittent compresses of solution of mercury bichloride, 1 to 4000. Auxiliary measures include administration of sedatives when itching is intolerable, or, in selected cases, brief treatment with cortisone or corticotropin. I am unconvinced that vitamin B complex expedites recovery from mucocutaneous monilial infection in otherwise healthy patients.

Finally, I must sound a note of caution concerning two agents commonly extolled for treatment of cutaneous moniliasis—methylrosaniline chloride and potassium permanganate. If used in low concentrations (no greater than 0.25% and 1 to 10,000, respectively), these items may successfully arrest the infection. But on an eroded or crusted surface, in the higher strengths commonly recommended, they sometimes lead to precipitation of an adherent coagulum which, by damming back secretions, may intensify the original eruption, and also, I have reason to believe, may contribute to the development of sensitization phenomena of other areas of the skin.

COMMENT

The primary objective of this report is to focus attention on the "forgotten man," the husband who is the recipient of genital dermatitis from his wife infected with C. albicans. The literature § makes out conjugal contagion of moniliasis to be an infrequent event, but cases which have come to my attention during the past few years satisfy me that this is not a rare means of transfer of monilial infection. In view of the fact that in each instance the man was in apparent good health, and because of the likelihood that the virulence of C. albicans is not accentuated by pregnancy or antibiotic therapy, it seems probable that transmission of infection was effected simply by exposure to increased numbers of organisms which under normal circumstances reside as harmless saprophytes in the vagina. None of the male patients related a history of similar disease antecedent to the infection of the wife. The onset of infection in these men shortly after treatment of the wife with broad-spectrum antibiotics, or during her pregnancy, the presence of characteristic signs of monilial vulvovaginitis in the wife, the clearing and relapse of genital dermatitis in the husband coincident with that of the vulvovaginitis of the wife, all argue persuasively a readiness of communicability not ordinarily associated with an innocent and casual saprophyte. Many reports attest to the proof of contagion in infections caused by C. albicans. What I have stated merely underscores the clinical observation that

§ References 4 and 5.

whenever the organisms proliferate to an extraordinary degree, they may assume the role of pathogens and invade previously normal, exposed skin and mucous membrane.

The contention of certain authors that the finding of Candida is not in itself diagnostic of the disease moniliasis is irrefutable. But when the presence of Candida coincides with the appearance of a dermatitis clinically consistent with one attributable to C. albicans, the causative relationship is not airily waved aside. The fact that excessive numbers of Candida may occupy the vagina without evidence of pathologic tissue reaction in some cases does not negate the observation that just such a numerical increase of Candida may in other cases be the sole reason for appearance of lesions. My material shows that not only may evidence of disease appear in the patient herself, but it may even be communicated to previously healthy skin of the genitalia of the conjugal partner by sexual contact. One cannot therefore maintain that increased numbers of Candida in the vagina may not cause disease in certain patients because they may be present asymptomatically in others, or that they cannot by overwhelming numbers alone cause cutaneous disease in a previously healthy male contact even though lesions are not visible in the female.

Needless to say, most of the time moniliasis is not transmitted freely by sexual exposure, as the frequency of genital moniliasis in the female compared with the infrequency of genital moniliasis in the male will affirm. Perhaps there is a greater natural immunity of the male genitalia to invasion by C. albicans, owing at least in part to superior aeration of the skin of the external genitalia. Perhaps more important for requirements of contagion is the presence of a mucosal focus of monilial infection, demonstrably capable of macerating the skin of the vulva and contaminating it with a continuous discharge of large numbers of C. albicans. In defense of this suggestion is the observation that when an unmedicated vaginal tampon is constantly worn, the vulvitis often heals with little or no local treatment.

SUMMARY

Simultaneously with an increased incidence of vulvovaginal moniliasis following the administration of broad-spectrum antibiotics in women, there has appeared in my practice an increased incidence of genital moniliasis in men. Sexual communicability of the infection caused by C. albicans was demonstrated in this study of nine married male patients. In each case, the disease was acquired from the wife, who had developed vulvovaginal moniliasis during pregnancy or after treatment with broad-spectrum antibiotics. Clinical manifestations of genitocrural moniliasis in female and male patients are described, and treatment of the infection is outlined.

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BRIEF HISTORY OF INDUSTRIAL DERMATOLOGY

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MORE THAN 250 years ago, there first appeared a remarkably accurate book devoted entirely to occupational diseases.[1] The author and "Father of Industrial Hygiene," Bernardino Ramazzini, displayed an uncanny insight into the detection of the personal hazards of the various occupational trades of his day. Hippocrates had previously written that the physician in his first interview with a patient should inquire into the chief complaint, what appeared to be the cause, how long had been the duration, and how the appetite had been affected. It was Ramazzini who, in 1700, first emphasized the importance of an additional question to be asked of the patient: "What is your occupation?" He spent many years gathering first-hand information by inspecting the workhouses and the tradesmen practicing their arts. He learned that a midwife might contract syphilis by attending an infected mother; that stasis ulcers often occurred in those who must stand at their work; that sailors of the day were usually covered with pediculi, and that soap makers were frequently afflicted with contact dermatitis due to the handling of strongly acrid materials. He described the case of a young gilder who died of mercurial poisoning from inhalation. He predicted that the use of tobacco would be continually condemned, yet forever used, by man. It was noted even then that cutaneous afflictions comprised a great portion of all the occupational diseases.

Although cutaneous diseases occurring in industry two and one-half centuries ago were known to be considerable, the imagination can scarcely conceive the scope this subject covers today. Much of the panorama of our present civilization has been made possible through its infinite technological achievements, but this has also unfortunately been paralleled by a simultaneous increase in those physical afflictions invariably associated with new chemicals and new processes.

Let us trace briefly some of the high points occurring in the history of industrial dermatology. It should be noted that many industrial dermatoses were already well under consideration long before our present generation.

OUTSTANDING CONTRIBUTIONS

E. Kaempfer, in 1712, apparently was the first to describe what was definitely an occupational dermatitis, and it was due to lacquer varnish.[2]

In 1775, chimney soot was first associated with occupational cancer of the scrotum observed among chimney sweeps by Percival Pott.[3]

Ackermann, in 1780, cited skin diseases that were due to dusty occupations.[4]

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From the Department of Dermatology and Syphilology of The Medical College of Alabama.

Robert Willan described dermatitis among shoemakers due to the wax used in their trade.[3] His classic dermatologic nomenclature won for him a gold medal in 1790.[5]

Early in the 19th century, Thomas Bateman described masons' itch caused by contact with lime.[6] He also was the first to describe lichen urticatus, molluscum contagiosum, and ecthyma.[5]

S. C. Turner Thackrah described dermatitis among tobacco workers and emphasized the prophylactic value of personal cleanliness in preventing industrial dermatoses.[3]

The French writer Ibrelisle noted that anthrax was spread by imported hides.[3]

In 1839, Cazenave and Schedel observed that excessive perspiration predisposed the worker to occupational dermatoses.[3]

Cless, in 1842, wrote of the obstinacy of the dermatitis that was so common among bakers.[6]

In the middle of the 19th century, Hebra and Kaposi made important contributions toward the differentiation of skin diseases due to external influences and those caused by inherent peculiarities or by systemic illnesses.[6]

Lespian described dermatitis due to coal tar in 1859.[3]

Three years later, Bazin made a classification of the known causes of occupational dermatitis.[3]

In 1863, Becourt and Chevalier reported that ulcerations might develop from contact with potassium bichromate.[6]

By 1876, there was published Koch's discovery of the organism that produced anthrax, which is seen more often among butchers, tanners, and woolsorters.[5]

The patch test was introduced in 1895 by Jadassohn, and this has proved to be a most significant landmark in its influence upon present-day dermatologic thinking.[7]

Charles White, in 1896, appears to have been the first in America to point out the importance of occupational dermatoses, and this was noted when he commented on dermatitis venenata "in the arts."[8] It is unfortunate that thereafter knowledge of and interest in the industrial dermatoses were not awakened in this country for another quarter century.

In England since the beginning of the 20th century, the following writers, to mention only a few, have made many valuable contributions: McLeod, R. Prosser White, Bridge, Sequeira, and Percival.[3]

In 1923, the necessity of recognizing certain fundamentals for the differentiation of occupational from nonoccupational dermatitis was first stressed by C. Guy Lane.[9]

In 1924, R. P. White pointed out the dangers associated with the use of paraphenylenediamine and quinone in the fur industry.[10]

C. Guy Lane, in 1925, urged a greater knowledge of fundamental cell and tissue processes and more basic research in order that the cause, therapy, and prevention of occupational dermatitis might be more rationally attacked.[11]

In 1926, White also wrote that the vast majority of trade eruptions were due to direct mechanical or chemical injury or irritation.[12] He pointed out that the various eruptions that might be produced could include an epithelioma, erythema, folliculitis, ulcer, eczema, or other manifestation.

In 1928, Dr. Lane recommended that the following standards be emphasized:

1. Investigation of the individual case, including an accurate history of the disease and the work, together with a careful examination

2. Familiarity with occupational processes and substances in the particular plant with which the patient is affiliated

3. Familiarity with the diagnosis and treatment of the most common skin diseases [13]

In 1929, Overton wrote that alkalis, degreasing agents, paraffin, petrol and naphtha, sugar, bakers' dough, dyes, and accelerators were the important causes of occupational dermatitis.[14]

Dyson pointed out, in 1929, that hyperhidrotic, xerodermatous, and ichthyotic subjects were more susceptible to trade dermatitis than normal subjects.[15]

In 1932, Downing deplored the lack of interest in America regarding the field of industrial dermatitis.[16] Very shortly thereafter, however, he was to see the literature on the subject become voluminous.

In 1932, Osborne and Putnam emphasized that there is a latent period between the first and subsequent exposures to a substance before an occupational dermatosis attributable to allergy may develop.[17]

Becker, in 1934, pointed out that occupational dermatoses usually occur on exposed areas and tend to be diffusely spread over the areas involved.[18]

It is unfortunate that, in 1934, Dr. Robert Prosser White died just prior to the publication in London of the fourth edition of his excellent and authoritative text on "The Dermatergoses or Occupational Affections of the Skin." [19]

In 1934, Wolter emphasized that daily contact with an antigen may produce spontaneous desensitization, whereas in an interval free from exposure, contact eczema may develop later due to return of sensitivity.[20]

In 1935, Malespine, in a report concerning eczema attributable to the various woods, pointed out the difficulties in the terminology of such woods as ebony, olive, rosewood, teak, and cocobola.[21]

Frank, in 1935, reported sensitivity to beef fat in a packing-house worker.[22]

In the next few years there appeared a tremendous increase in the number of specific case reports listing reactions to new industrial agents and processes. Of more importance, however, was the fact that this period brought agreement upon the basic thinking on some of the fundamental problems concerned in occupational dermatology. Because of their importance, several of these considerations will be listed.

In 1936, Sulzberger was the first to enumerate basic rules useful in determining the industrial nature of certain dermatitides.[23] He delineated the criteria needed for establishing proof of the probable industrial nature of a given dermatitis and described possible diagnostic pitfalls.

In 1936, because of increasing interest in industrial dermatoses and a need for a central clearing house of information, both the section on Dermatology and Syphilology of the American Medical Association and the American Dermatological Association appointed committees to undertake a co-operative consideration of industrial dermatologic problems.[24] In a subsequent report, certain definitions and criteria were listed:

An occupational dermatosis was defined as a pathological condition of the skin for which occupational exposure can be shown to be a major causal or contributory factor.

This statement was made regarding a primary irritant:

> When a substance in a given concentration in a given vehicle and in a given manner and length of exposure produces a clinically manifested irritation on the skin of a majority of persons not previously sensitized to that substance, that substance is a primary irritant under the specified conditions.

A sensitizing agent was defined as one which increases the capacity of the tissues to react to subsequent exposure.

Hypersensitivity was defined as a condition in which the tissue has a greater capacity to react than the norm.

Detailed criteria for the diagnosis of occupational dermatoses were also given.

Hausser, in 1938, emphasized the common occurrence of folliculitis and pyoderma due to lubricating oils.[25]

During the same year, Stevens and Jordani reported five cases of sensitivity to jute, the vegetable fiber grown in India, which is commonly used in the form of burlap.[26]

Klauder, in 1938, showed erysipeloid to be an occupational disease.[27]

Schwartz and Warren advised, in 1939, that an insecticide causing one case of dermatitis in 200, after 15 minutes daily exposure for 10 days, should not be placed on the market.[28]

In 1939, Foerster and Schwartz, in an excellent report on pitch dermatitis and melanosis occurring in the pitch and tar industry, pointed out that these conditions were attributable to true photosensitization and not contact sensitization or allergic predisposition.[29]

Reale, in 1939, in a study of 800 salt-mine workers, noted that they occasionally developed a dermatitis from the necrotic, caustic, and mechanical action of salt in contact with the skin.[30]

H. Haldin-Davis, in 1939, described chloracne due to the insulating material, perchlornaphthalene or "perna," in electrical workers.[31]

F. T. Becker observed, in 1940, the first four cases of milkers' nodule described in America.[32]

DERMATOPHYTOSIS IN INDUSTRY

It has been reported that dermatophytosis among the industrial population is no greater than among the local population of the same area.[33] Peck and his associates are of the opinion that a dermatophytic infection or a dermatophytide is not particularly important in time lost by industrial workers.[34] They do not believe that an allergy to fungi or their products appears to predispose to the development of an allergic contact dermatitis. Downing and Messina, on the other hand, believe that a dermatophytid present on the hands may lower the local resistance sufficiently to allow industrial mechanical and chemical contacts to aggravate the original eruption.[35] Ayres and Anderson stated that an unproved diagnosis of a fungous infection of the hands is likely to be right only 12% of the time.[36]

CANCER OF THE SKIN AND OCCUPATIONAL TRAUMA

The incidence of occupational skin cancer reported in this country is low, but records do not reveal its true occurrence.[37] Creosote, coal tar, soot, anthracene, arsenic, roentgen rays, and ultraviolet are a few of the many known agents said to be potent sources of cutaneous cancer seen in industry.[38] Whether a single accidental injury can cause human cancer is a moot question.[35] Wynder has pointed out that 2,975 cases of industrial cutaneous cancer had been reported in Great

Britain by 1945, whereas only 151 cases had been reported by 1948 in this country.[39] Exposure to pitch, tar, shale oil, mineral oil, and bitumen were the principal contributory causes in Great Britain. It is probably true that a much greater number would have been reported had there been instituted a better system of recording and reporting cases.

THE PATCH TEST

J. Jadassohn introduced the patch test in 1895, and our knowledge of the test was in turn further developed by Bloch.[40] In 1920, it was first used in animal experimentation in this country by Markley.[40] The performance of the test is a simple procedure, yet the pitfalls in its proper execution and interpretation are many. If properly understood, it can be of great value as a diagnostic aid. Sulzberger and Wise, in 1931, pointed out its uses, advantages, and limitations.[7]

Downing and Messina noted, in 1946, that since patch testing cannot simulate the sweating, friction, and other factors to which a worker is subjected, its value is limited.[35]

Morris remarked, in 1953, that irritants should not be used for patch testing; that all materials must be properly diluted, and that the eczematized skin has a lower threshold of irritability than does the normal skin.[41]

Bechet, in 1939, reported two cases in which the patient developed a generalized eczematoid dermatitis within 48 hours after a strongly positive patch test and emphasized its possible danger in certain cases.[40]

Kulchar, in 1941, reported a delayed reaction of 45 days to a patch test and emphasized the importance of the delayed reaction.[42]

Schwartz and Campbell, in 1947, showed that preemployment patch tests are not practicable or advisable and may actually sensitize the worker.[43] It is known that sensitization is acquired by contact. Usually seven days or more must elapse between the first contact and the time when sensitization is established.

"HARDENING" IN INDUSTRIAL ALLERGIC DERMATITIS

In 1923, J. Jadassohn described a term which represents one of the peculiar allergic phenomena.[44] The term, "hardening," is used to indicate a condition in which an allergic contact type of dermatitis in sensitized persons disappeared or failed to reappear on repeated exposure in industry to the sensitizing chemical.[45] It may be permanent. However, in most cases, if exposure is discontinued for a period of time, sensitivity returns. Practically all industries which have cases of allergic dermatoses have noted examples of hardening. This development may vary in degree and may complicate patch test interpretation.

WORKMEN'S COMPENSATION LAWS

Workmen's compensation laws should afford consistent and immediate aid for workers, and, simultaneously, should prevent employers from being assessed unlimited liability. The first compensation law in this country was passed about 1908.[46] In the beginning, only accidents were covered. Later, compensation for certain occupational diseases was also included. In this country, workmen's compensation laws exist in all the 48 states and in all the territories of the federal jurisdiction. Occupational diseases are covered in 41 of the 48 states. Only in a few states is the coverage adequate for all the occupational diseases.

Harvey, in 1933, requested the cooperation of expert chemists and physicists as well as employers and employees to do their best in handling the economic and hygienic questions involved.[38] Foerster, in 1936, deplored the almost complete lack of opportunity for the medical profession to participate in the designing and enactment of the various laws and the provisions for their application and interpretation.[47]

Lane, in 1937, urged that more uniform legislation be passed in the various states.[48] Traub and Schultheis urged greater cooperation between employers or insurance carriers and the physicians treating patients with industrial dermatoses, in order that many of the present shortcomings might be eliminated.[49] Campbell, in 1951, pointed out that since more than 60% of all occupational ills are due to industrial dermatoses, their understanding and control must be a considerable factor in a progressive industrial hygiene program.[50]

CLASSIFICATION OF IRRITANTS

There is little to be added to the classification of irritants published in 1932 by Downing and Welch.[16] These were listed as follows:

1. Mechanical or physical agents—abrasives, heat, cold actinic rays, friction
2. Flowering plants and their products—resin, lacquers, wood dusts
3. Vital Agencies
   - *a.* Bacteria, yeasts, molds
   - *b.* Members of the animal kingdom
4. Chemical Agents
   - *a.* Inorganic compounds—acids, bases, salts
   - *b.* Hydrocarbons and crude coal tar products—oils, tar, pitch
   - *c.* Other organic compounds

PREDISPOSING CAUSES OF OCCUPATIONAL DERMATITIS

Schwartz, in 1950, listed the predisposing causes of occupational dermatitis.[51] These include the following:

1. Lack of personal and environmental cleanliness
2. Excessive perspiration due to any cause
3. Presence of other skin disorders which impair the natural defensive mechanism of the skin
4. Allergy, which is thought to account for less than 20% of all occupational dermatoses

PROPHYLAXIS

Much has been written concerning the prevention of industrial dermatoses.* Some of the more significant contributions merit enumeration:

Preplacement examinations are needed to prevent workers with cutaneous abnormalities from being placed in occupations associated with unavoidable skin hazards.

Adequate ventilation and removal of unnecessary hazards are essential.

Employee instruction concerning skin hazards and preventive measures is needed.

Adequate protective clothing should be provided.

Complete removal of irritants by harmless methods several times per shift is to be recommended. Adequate washing facilities must be provided, since the personal cleanliness of the worker is important.

* References 3, 19, 33, and 43.

A periodic reexamination of hands and arms is indicated, in order that minor injuries may be treated immediately.

The presence of adequately trained experts may foresee and prevent future industrial illnesses.

Protective ointments are low on the list of preventive measures, yet they may at times be the only available means of protection. Patients generally like to use them.[38] Since the worker removes the ointment by washing after work, fortunately he also usually removes whatever irritants may have been on his skin.

COMMENT

During and since World War II, industry in the United States has continued to be plagued with many varieties of industrial dermatoses. These are estimated to cost annually at present more than $100,000,000.[51] The majority of these have been attributable to contact with one of the following: cutting oils, solvents, greases, rubber and its compounds, strong soaps, alkalis, cements, acids, trauma and accidental injury, physical and biological agents.†

The growth of chemistry has so increased the liability to occupational dermatoses, that a complete list of agents would be astronomical. Although allergy plays a prominent role in industrial dermatoses and accounts for some of the most difficult problems, nevertheless primary irritants are responsible for 80% of contact occupational dermatoses, and sensitizers for only 20%.

In conclusion, it should be reiterated that although much has been learned about occupational dermatitis, unquestionably, much more remains to be explained. Let us not forget our debt to men like Fordyce, Lane, Foerster, Downing, Sulzberger, Schwartz, Peck, and many others. Further investigation into the field of industrial dermatology or the "dermatosis industrialis" of Lane or the "ergodermatoses" of Downing offers a true challenge to us all.

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MICROSCOPIC STUDIES OF FETAL AND MATURE NAIL AND SURROUNDING SOFT TISSUE

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KNOWLEDGE of nail disease is indeed limited. Two textbooks* have been published on this subject in the last quarter of a century, but a study of the table of contents of both reveals merely a list of the many diseases in which concomitant nail findings have been reported. The descriptions are for the most part those of gross morphologic changes in the nails. Only a few isolated reports are available concerning the correlative histology of conditions that affect the nails, and the value of these reports is lessened by the lack of adequate histologic studies of the normal nail. As a matter of fact, most of us speak glibly of "nail disease" without having given thought whereof we speak. Some refer to paronychial disease with secondary change in the nails as nail disease; this is certainly confusing in view of the present concept of nail generation from the matrix (proximal nail bed). Various conditions, systemic and local, may affect the matrix, the pink portion of the nail bed, the nail plate, the paronychium, or other anatomic units of the nail and its environs. A certain disease may always select a single anatomic portion of the nail for involvement. A classification of nail disease based on the anatomic unit of the nail or surrounding soft tissue which is involved seems most desirable. Until a clearer picture of the normal nail in situ is available, interpretation of the many nail changes seen daily cannot have meaning. The presentation to follow includes histologic observations and certain concepts of the development of the nail resulting from the study of a large series of normal digits.

Why has there been no thorough anatomic study of the normal nail to serve as a foundation for the study of nail disease? The answer lies in the difficulty in obtaining normal specimens and in the prohibitive histologic techniques which have required prolonged decalcification with, for example, nitric acid because of the presence of the bony phalanx. Despite decalcification, sections were still poor, and the decalcification always endangered histologic detail. I was fortunate to have at my disposal a steady supply of amputation specimens obtained at the Mayo Clinic

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Abridgment of thesis submitted by Dr. Lewis to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology. Work done in the Section of Dermatology, Mayo Clinic, with the assistance of Drs. P. A. O'Leary and Hamilton Montgomery; in the Section of Pathologic Anatomy with the assistance of Dr. J. W. Kernohan, and in the Section of Anatomy with the assistance of Dr. W. H. Hollinshead.

* References 1 and 2.

in the treatment of such conditions as neoplasms of the proximal parts of the extremities and injuries of the limbs. The second major obstacle was overcome by the mechanical removal of the bony phalanx before submitting the specimen for routine sectioning. In order to understand the mature nail, it is necessary to have a working knowledge of the embryonic nail. To this end, a chronologic series of fetal digits was prepared and studied.

It is necessary to clarify certain terms which are used frequently in the accompanying presentation.

The three edges of the nail inserted into the soft tissue rest in a depression termed the nail fold (nail groove, nail sulcus, nail furrow); the skin extending from the fold over the nail is called the nail wall. The thin membrane extending from the proximal wall a short distance over the nail is the eponychium. The lunula is the convex lens-shaped whitish opacity which may be seen distal to the eponychium. The paronychium is that portion of the soft tissue surrounding the nail border, whereas the perionychium consists of the paronychium plus the nail bed.

The nail fold is divided into a dorsal roof and ventral floor by the nail root proximally and by the flanking borders of the nail laterally. The nail bed comprises all of the soft tissue immediately beneath the nail plate (nail body).

The distal portion of the nail is subtended by a mass of keratin, the hyponychium.

The anterior limiting furrow (distal limiting furrow) is a crescent-shaped depression in the dorsal surface of the digit immediately distal to the hyponychium.

A longitudinal vertical section (sagittal section) is one paralleling the long axis of the digit and perpendicular to the nail plate.

A transverse vertical section is one cut perpendicular to the long axis of the phalanx.

It is regretted that, in order to prepare this paper for publication, many features of anatomic interest, including photomicrographs, had to be deleted from the original thesis.[3]

Several reports of past work on the normal nail are recommended to the reader.†

MATERIALS AND METHODS

Fingers and toes from amputation specimens and fetuses were studied in histologic section with various stain techniques. In general, serial, semiserial, or multiple sections were reviewed. The material studied included 45 specimens. These consisted of one 6-week fetus in serial section, 6 hands and feet in serial section from fetuses at approximately the 2-month stage, and 16 digits in serial and semiserial section from fetuses ranging from the 3-month to the 9-month stage. Adult specimens studied included 1 toe in transverse serial section, 1 toe in longitudinal serial section, and 20 digits, fingers and toes, in multiple section.

Of primary importance was the method used to circumvent the decalcification required by the presence of the terminal bony phalanx. The method was worked out in collaboration with Dr. R. A. Groat, Section of Anatomy, Mayo Clinic. A scalpel was used to excise the soft tissue exposing the entire ventral surface of the distal bony phalanx. A 6 mm., round, cutting fenestration burr for use with the dental handpiece was employed. The phalanx was pulverized by grinding with the burr. This procedure obviated in almost all cases the necessity for decalcification, thus preserving better histologic detail. It was not necessary to apply the foregoing procedure to fetal tissue because of the softness of bone.

† References 4 through 17.

Histologic material was stained by the following techniques: (1) hematoxylin and eosin, (2) van Gieson's, (3) elastin H, (4) Gömöri's reticulum, (5) Maresch-Bielschowsky, (6) silver protein (modified after Bodian and Moskowitz), (7) Masson's trichrome, (8) Hotchkiss-McManus, (9) acid orcein Giemsa, (10) periodic acid Schiff, (11) von Kossa, and (12) Mallory's phosphotungstic acid.

All specimens, amputation and fetal, were placed in 10% formalin solution prior to sectioning except for the occasional employment of absolute alcohol. Routine processing of tissue consisted of dehydration in alcohol and acetone, clearing in xylene, and embedding in paraffin.

Procedure.—Details of the procedure are as follows:

1. Fix in 10% formalin
2. Dehydrate

   First day. Immerse in 70% ethanol for 24 hours

   Second day. Immerse in 80% ethanol for 24 hours

   Third day. Immerse in 95% ethanol for 4 hours (8 a. m. to 12 noon); immerse in absolute acetone for 4½ hours (12 to 4:30 p. m.); immerse in absolute acetone for 15½ hours (4:30 p. m. to 8 a. m.).

   Fourth day. Immerse in xylene for 1 hour (8 to 9 a. m.)
3. Infiltrate with paraffin

   Allow to remain in paraffin at 60 C. for 52½ hours (9 a. m. of the fourth day to 1:30 p. m. of the sixth day)

   Embed in fresh paraffin
4. Section. Cut down paraffin blocks to the desired size and soak in tap water overnight. Place block in the microtome so that the nail side is at the top of the block and is cut last
5. Stain. Routine procedures are used; however the tissue on the slides is coated with celloidin as follows: deparaffinize with xylene; remove xylene with absolute methanol; cover tissue with a thin coating of celloidin (1% in equal parts of ether and absolute ethanol); dry; place in 50% methanol and continue staining. When cover-slipping, a fine camel's hair brush dipped in xylene is used to brush down the curled edges.

THE FETAL NAIL ‡

Separated digits are discernible in the eighth week of fetal life. By the tenth week, the most striking feature to be found in study of the distal part of the digits in the region of future nail development is what will be called the dorsal plume (Fig. 1*a*). This structure has been referred to in the past as the *sohlenhorn* or sole plate by the comparative anatomists. This term is misleading because it suggests a site other than the true dorsal location of this organ. The dorsal plume is found on the distal portion of the dorsal surface of the digits, where it appears to be mushroom-shaped.

The base of the dorsal plume is made up of 10 to 12 layers of horizontally arranged, spindle-shaped, partially keratinized cells capped by a dense array of keratohyalin-like granular activity. This region is marked by countless granules varying greatly in size and infiltrating a transitional zone wherein large vesicular cells are developing. These large cells form the umbrella-shaped portion of the

‡ Dr. J. W. Kernohan, Section of Pathologic Anatomy, Mayo Clinic, provided the amputation specimens and fetuses. Technical assistance was rendered by Mrs. M. Noser and Miss F. Lehman of the pathologic anatomy tissue laboratory and by the Misses V. Anderson, D. Zweck, and O. Elford of the pathology museum, Mayo Clinic.

mushroom, best termed the pileus from the Latin for that botanical entity. The cells possess a clear cytoplasm and, when present, nuclei that are polymorphous and deeply staining. In many instances the cells are without nuclei or contain in their stead large eosinophilic, amorphous masses. A desquamative process of the periph-

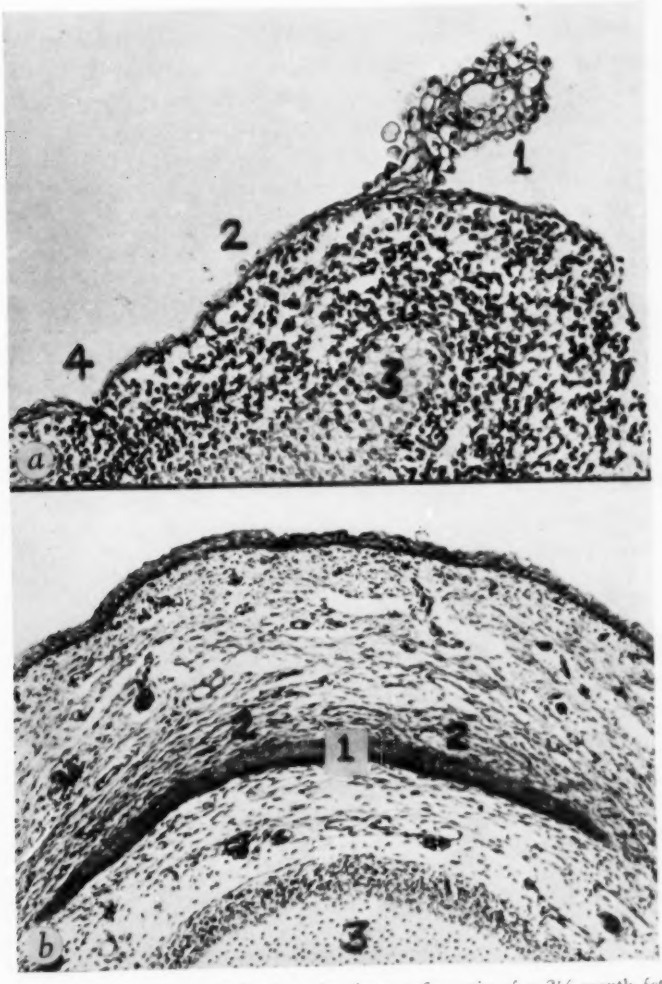

Fig. 1.—In *a* is shown a longitudinal section from a fingertip of a 2½-month fetus (hematoxylin and eosin; × 210). *1*, Dorsal plume; *2*, future nail bed; *3*, bony phalanx, and *4*, suggestion of future nail fold. In *b* is shown a transverse section from a finger of a 3-month fetus through the proximal end of the proximal nail fold (Masson trichrome stain; × 100); *1*, fold; *2*, perionychial condensation of mesenchyma, and *3*, bony phalanx

eral cells is noted. The keratohyalin-like granules referred to previously do not stain with the Hotchkiss-McManus technique and therefore presumably do not contain polysaccharide.

The height of the dorsal plume approaches the dimension of the cross-sectional radius of the digit at its point of attachment.

The microscopic anatomy of the epitrichium and precollagen mesenchyma is presented in the unabridged thesis.

Sections from the 3-month fetus reveal that the nail fold has definitely begun its development with lateral and proximal invagination. Its periphery in all directions is made up of basal-type cells and its body of squamous-type cells. In transverse, vertical section (perpendicular to the long axis of the phalanx) serially distalward, the first evidence of the proximal end of the nail fold is a horizontal linear streak of epidermal cells centered in a superiorly convex arch of somewhat condensed connective tissue having its ends at the phalangeal equator (Fig. 1*b*). Beneath the fold are many large horizontal capillaries. Proximal to the invaginating fold is a fibrous condensation, and proximal to the condensation, a mass of large vascular lakes.

The onychogenic area in the nail fold reveals two predominant types of nail-precursor cells. The first, representing a change from the resting epidermal cell, is a swollen clear cell with a pale, basophilic nucleus. The nuclear membrane is quite prominent. The periphery of the cell is densely eosinophilic. This cell is best termed the bulb cell. The next cell type, the void cell, is a bulb cell which has lost its nucleus and shows diminished eosinophilia and lesser thickness of the cell membrane. Following the formation of the void cell, the intercellular cytoplasmic processes tend to segment; this is followed by a straightening of the resultant annular and arcuate configurations. This produces what appear to be fine tubules, which eventually become less conspicuous as horizontal, eosinophilic, intercommunicating streaks in the nail.

The nail bed is at this stage a shallow depression limited distally by a crescent-shaped elevation of dermis and epidermis which forms the foundation for the dorsal plume (future hyponychium). This elevation might well be called the distal prominence (Fig. 2*a*).

Keratohyalin-like granular concentration is greatest in the epidermis of the eponychium, roof, and floor of the nail fold and the distal prominence. The thin lamellated keratin sheet overlying the nail bed appears to originate from the eponychium, proximal portion of the nail bed, and the lateral nail fold. Histologically, the possibility of generation from the distal portion of the nail bed is unlikely but cannot be categorically dismissed. What appear to be superficial fetal epidermal cells may be found on the surface of the generating corneous layer (Fig. 2*b*).

Study of the 3½-month fetus provides information particularly striking in regard to the connective tissue surrounding the proximal nail fold. It is seen to be stratified and to form a wedge embracing the fold. There appears to be no crowding of the tissue, suggesting that the proximal invagination of the nail fold is a mass movement of dermis as well as epidermis (Fig. 3*a*). This concept can be further amplified in transverse vertical section by demonstrating horizontal, evenly spaced, "collagen" layers proximal to the nail fold.

Sections from the 4-month fetus also demonstrate fetal epidermal cells upon the dorsal surface of the newly forming nail, suggesting that the nail is being formed beneath this presumably epitrichial layer or burrows beneath it from a proximally located generative source. The superficial cells in this location show pyknosis and karyorrhexis.

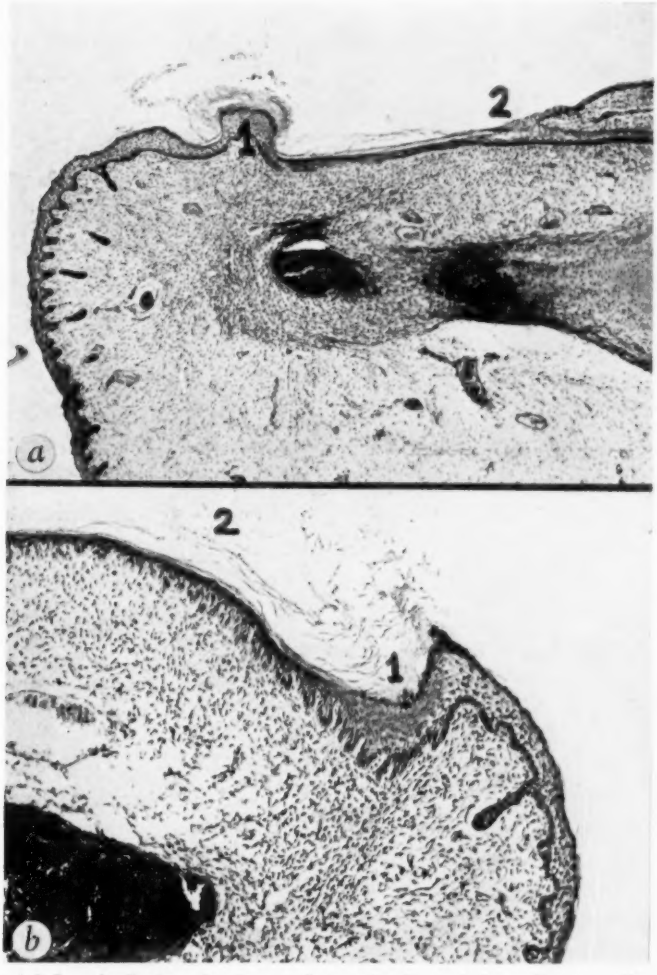

Fig. 2.—(*a*) Longitudinal section from a finger of a 3-month fetus (hematoxylin and eosin; × 55); *1*, distal prominence capped by the remnant of the dorsal plume, the future hyponychium, and *2*, keratogenesis by the distal margin of the eponychium. (*b*) Transverse section from a finger of a 3-month fetus distal to the eponychium (hematoxylin and eosin; × 115). *1*, keratogenic activity in the lateral nail fold; the fine black dots seen on the surface of the keratin at *2* appear under higher power to be fetal epidermal cells of the epitrichial type, suggesting the interposition of cornified material between these cells and the subjacent epidermis.

In the 5-month fetus, the nail is seen to be made up of two separate layers. This is the earliest stage of development at which the nail unit (nail plate) is seen to be made up of more than one component.

The eponychium no longer produces corneous lamellae as it did in earlier fetal life when these lamellae covered much of the nail bed.

The epidermis of the lateral nail folds shows much keratohyalin-like granular activity and the formation of cornified material. These take place from the proximal

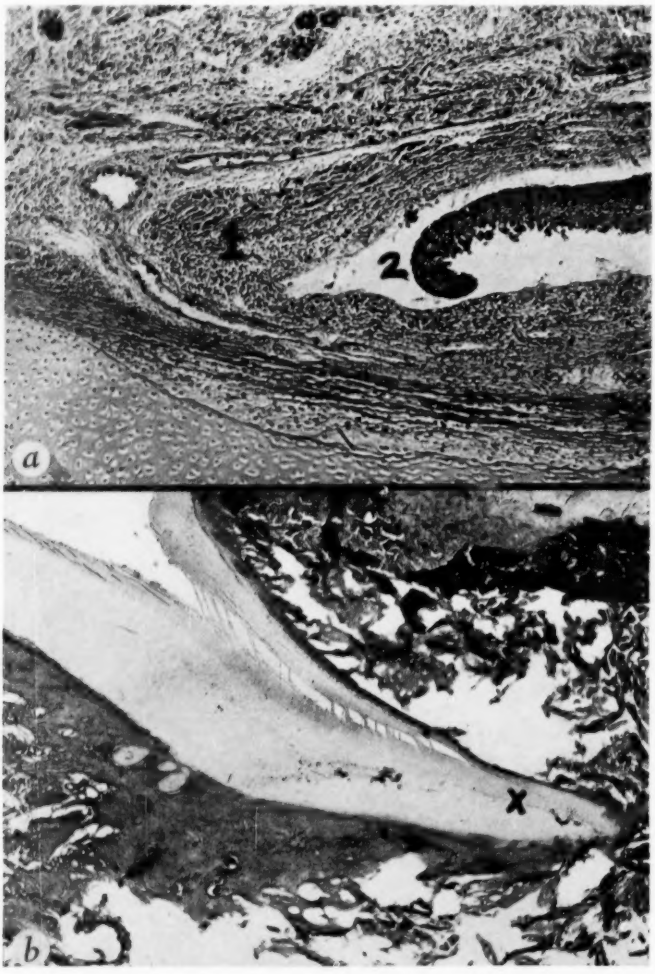

Fig. 3.—(*a*) Longitudinal section from a finger of a 5-month fetus (elastin H stain; × 130). *1*, Dermal wedge proximal to *2*, the nail-fold epidermal invagination. Note the conformance of the vasculature to the wedge shape. (*b*) Longitudinal section through the proximal nail fold of an adult toe (hematoxylin and eosin; × 30); *x*, darker-staining dorsal nail arising from the proximal one-fourth of the roof of the fold.

nail fold to the distal emergence. This term is introduced to denote that anatomic landmark created by the junction of the free edge of the nail and the lateral border of the nail.

The anticipatory wedge of connective tissue providing a proximal buttress for the nail fold invagination is still well shown. The conformance of the vasculature to the dermal pattern is well shown in Figure 3*a*. The soft-tissue invagination may extend as far proximally as the distal interphalangeal joint. The large vessel seen immediately proximal to the wedge is seen in serial sections to communicate with the joint. This anatomic relationship is of value in considering the close association between joint and nail disease.

At term, the nail may be seen to be composed of three layers. The superficial layer is called the dorsal nail, the main nail body, the intermediate nail, and the deepest layer, the ventral nail. The thickness of the dorsal and ventral nails when contrasted with that of the intermediate nail approximates with great variation the ratio of the thickness of the epidermis when compared with the dermis. In the term specimens studied, the dorsal nail persisted to the free margin of the nail.

The silver protein-staining technic, modified after Bodian and Moskowitz, produces the greatest color contrast between the various nail layers.

The dorsal nail originates from the proximal portion of the roof of the nail fold by a process of, first, macrocytosis (swelling of the cell), next, nucleolysis (disappearence of the nucleus), and, finally, cell collapse (a flattening of the cell). The cycle is thus one of inflation and deflation. The resulting flattened cell takes its place in the flattened lamellae of the nail unit.

The intermediate nail arises from the floor of the nail fold by a process best termed gradient parakeratosis, whereby the epidermal cells undergo progressive broadening and flattening with prolonged retention of nuclei. In the lateral nail folds is found a histologic suggestion that the dorsal nail and occasionally the intermediate nail are drawing some of their substance from keratinized material generated in the folds.

The ventral-nail layer, when present, is first observed in the fetus near term. It arises usually from the nail bed underlying the distal one-half to two-thirds of the roseate nail. The latter term is introduced to describe the nail between the distal border of the lunula and the proximal margin of the whitish opacity at the free edge of the nail. The fetal ventral nail arises from the epidermis by a rather abrupt bulb-void cell sequence, but in mature specimens the generative process is quite similar to that of the dorsal nail, that is, inflation-deflation.

In progressively distad transverse serial section, the proximal region of ventral nail appears in two portions divided medially and flanked laterally by intermediate nail. This indicates that the proximal margin of this deepest nail layer either grossly parallels the distal margin of the lunula or presents a fishtail bifurcation.

THE MATURE NAIL

The nail unit, in general, consists of closely united but poorly defined lamellae. Each lamella is composed of one or more layers of flattened epithelial cells forming scales or plates.

The dorsal nail in the adult digit is seen in the midline vertical longitudinal section to take origin from up to one-sixth of the proximal portion of the floor of the nail fold and up to one-half of the proximal portion of the roof of the fold

(Fig. 3*b*). The mechanism of onychogenesis is that of the inflation-deflation cycle described in the section on the term fetus. Granulations which simulate but which are much fainter than keratohyalin may be found in the generative cells.

The basophilic dorsal nail is frequently retained in an irregular "patchwork" manner to the free edge of the nail but may disappear before this distal margin is reached. Lagermalm and co-workers,[18] in studying the skin and nail with the electron microscope, found evidence of an epicuticle. That found on the nail was more contaminated by extraneous material than that from the skin. The thickness of the membrane was estimated by palladium shadow technique to be 100 A. units. The relationship between this epicuticle and the dorsal nail will undoubtedly be established by future study.

Transverse sections stained with silver protein demonstrate that in general there have been less flattening and amalgamation of cells in the dorsal nail than in the intermediate nail. The continuity of the corneous material in the lateral nail fold with that in the dorsal nail raises the possibility of onychogenesis in this region.

As in the fetus, the thickness ratio of the dorsal nail to the intermediate nail in the central portion of the nail unit compares grossly in magnitude with that of the thickness ratio of the glabrous epidermis to the dermis (Fig. 4*a*).

The intermediate nail, or main nail body, takes origin from the epidermis of the nail bed bounded by the distal margin of the lunula and the most proximal portion of the floor of the nail fold. Occasionally, as has been mentioned, the dorsal-nail generative area may include up to one-sixth of the proximal floor of the fold. The intermediate nail appears to originate from its generative epidermis by the process previously described as gradient parakeratosis. As in the fetus, this consists of a change in the superficial epidermal cells whereby they become flattened, resulting in an increase in surface area. There is a change from the eosinophilic hue of the epidermal cell to a colorless or even palely basophilic appearance. The nuclei tend to become smaller and, if retained in the intermediate nail, generally collect eosinophilic perinuclear material. Thus, two phenomena may be found in the intermediate nail: first, there may be horizontal streaking from flattened cell bodies or cell membranes, and second, persistent retained "parakeratotic" shrunken nuclei with perinuclear eosinophilic material or vacuolization. These latter elements might well be termed pertinax bodies from the Latin referring to their persistence in otherwise monotonous nail. The bodies are generally found in a galaxy longitudinally disposed from the middle of the proximal nail fold to the distal margin of the roseate nail.

The pertinax bodies tend to maintain the same depth throughout the length of the nail, suggesting that pathology of the roseate nail bed will not be reflected at the nail surface.

The conversion to nail from the gradient parakeratotic area may be very abrupt. This type of onychogenesis may be found occasionally but to a lesser degree in other areas of the nail bed.

The common border between dorsal and intermediate nails is rich in polysaccharide as demonstrated by the periodic acid Schiff technique. There is usually some intermingling of nail layers at the common boundary.

As briefly mentioned, the stain technic which most strikingly delineates the intermediate nail is that employing silver protein modified after Bodian and Moskowitz. This stains the intermediate nail a striking yellow-brown and the dorsal

and ventral nails, shades of blue-black. The ventral nail may show tints of red and brown. This technique also best demonstrates the cellular pattern of the nail lamellae.

The site of origin and the form of the ventral nail follow the description as given in the section on the term fetus. The ventral-nail generative process suggests

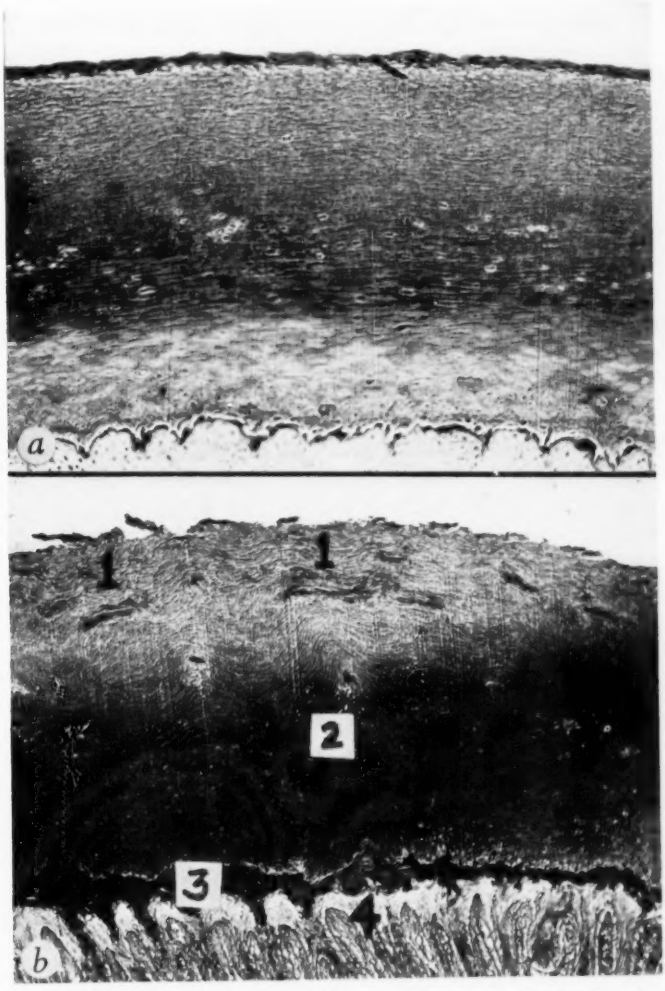

Fig. 4.—(*a*) Transverse section from an adult toe distal to the lunula. The darker superficial layer is dorsal nail (silver protein; × 120). (*b*) Transverse section through an adult toe proximal to the hyponychium (silver protein; × 65); *1*, persistent patches of dorsal nail; *2*, intermediate nail; *3*, ventral nail; and *4*, nail-bed epidermis.

that of the dorsal-nail inflation-deflation cycle. Keratohyalin-like granulation in the generative cells may not be marked and occasionally may not be seen. At its proximal limits, ventral-nail generation appears to be limited to the epidermal ribs, the longitudinal elevations in the nail bed distal to the lunula.

The thickness of the ventral nail is of similar order of magnitude to that of the dorsal nail (Fig. 4*b*); however, it may reach a maximum of one-third of the thickness of the intermediate nail. The ventral nail may be absent.

The common border between the intermediate and ventral nails is rich in polysaccharide although less so than that between the dorsal and intermediate nails.

It must be emphasized that separate and distinct dorsal, intermediate and ventral nail layers cannot be demonstrated in every specimen and that the contrast is more striking in toenails than in fingernails.

The hyponychium develops in a manner corresponding to that of the glabrous stratum corneum but contains many more eosinophilic vacuolated cells. These cells suggest their fetal predecessors, the large vesicular cells of the dorsal plume. These cells are present in both the fingers and the toes and are not stained preferentially by the periodic acid Schiff technique; hence, it is unlikely that they represent fungous spores as has been previously suggested. The evolution of the dorsal plume into the hyponychium may be followed in the study of sections from fetal and mature digits.

Occasionally the ventral nail is poorly developed so that it is difficult to resolve it and the hyponychium into two anatomic entities; however, the absence of eosinophilic vacuolated cells in the ventral nail aids in identification.

Many specimens (Fig. 5*a*) reveal mechanical separation between the nail unit and the hyponychium as a result of sectioning. In these instances, the hyponchium is retained in immediate apposition to the epidermis of the distal prominence.

Sandwiched between the dorsal nail and the distal portion of the eponychium may be found a stratified cornified plate which could be well termed the nail vest (Fig. 5*b*). It frays and disappears shortly after its emergence from the nail fold. This organ is pushed proximally with the eponychium during manicuring. The nail vest appears to arise entirely free from the roof of the nail fold. Portions of the vest may remain adherent to the surface of the dorsal nail for varying distances beyond the eponychium. The vest is also found in the lateral nail folds and here may extend medially onto the exposed nail.

The dorsal surface of the nail-bed epidermis presents longitudinal ribbing, which fits into corresponding furrows in the ventral surface of the nail unit. In the generative area of the intermediate nail, the ribbing is much less prominent and may be absent.

The epidermis of the nail bed distal to the lunula shows little to no generative activity, and this for the most part is restricted to the ribs. There seems to be a gradual change-over from a sluggish gradient parakeratosis to onychogenesis in the presence of keratohyalin-like granulation.

The epidermis at the base of the hyponychium, the distal prominence of the fetus, frequently distinguishes itself by presenting vacuolization of its cells. The prominence is greatly flattened beneath the mature nail.

The majority of the basal cells of the medial two-thirds of the nail-bed epidermis from the region of the distal margin of the lunula to the generative area of the ventral nail may lose both nuclei and cytoplasm but retain their original cylindric contour with the long axis perpendicular to the basement membrane. Laterally the basal cells resemble those of the glabrous skin. Progressively distad serial sections

show that in the generative epidermis of the ventral nail, the basal cells may show nuclei, and further distad, nuclei and cytoplasm. This alteration is noted in fetal specimens as early as the third month.

Rete ridges are an anatomic feature of the epidermis of the floor and lateral aspects of the proximal nail fold. The ridges are markedly increased in length distal to the lunula.

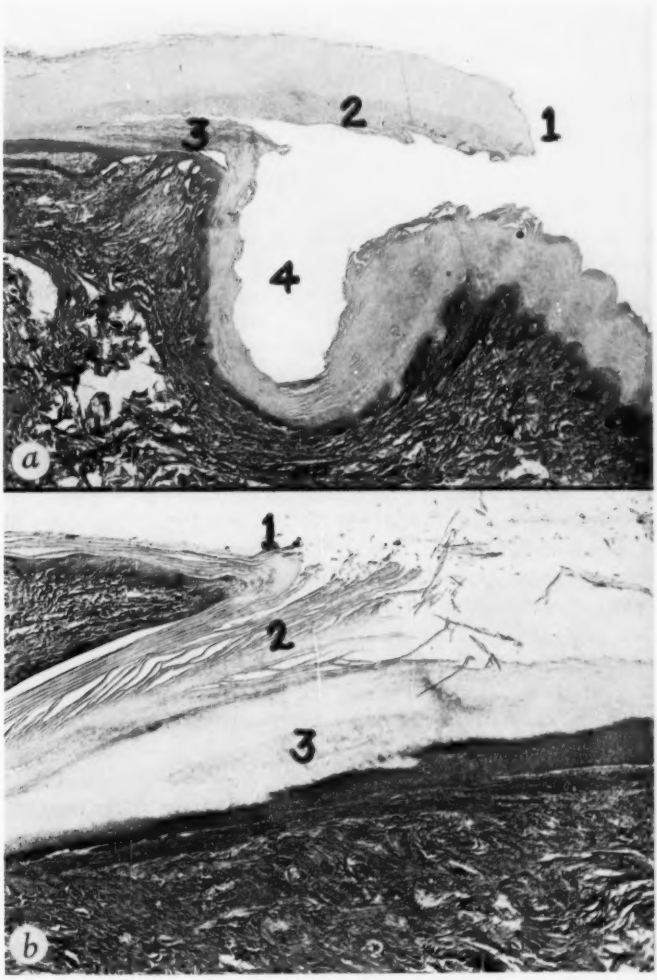

Fig. 5.—(*a*) Longitudinal section from an adult toe (hematoxylin and eosin; × 20); *1*, free edge of the nail; *2*, ventral nail; *3*, hyponychium; and *4*, exaggerated anterior limiting furrow. (*b*) Longitudinal section from an adult toe (hematoxylin and eosin; × 35); *1*, eponychium; *2*, nail vest, and *3*, staining artifact.

The dermis of the nail bed and nail wall is arranged in dorsally elevated waves reflecting the longitudinally disposed epidermal ribs. Heretofore these waves have been referred to incorrectly as papillae; they might well be named dermal ribs.

Elastic tissue in the dermis generally runs parallel to the long axis of the finger; in the dermal ribs, the elastic fibers run vertically. Several specimens have revealed a heavy concentration of elastic tissue beneath the anterior limiting furrow.

In contrast with the fairly orderly pattern of the elastic tissue, the reticulum fibers are seen in sections stained by the Mallory phosphotungstic acid technic to run in a helter-skelter manner; occasionally a vertical preference is seen in the nail-bed dermis and a horizontal preference in the nail-fold dermis.

Fat occasionally may be found in the nail bed, especially beneath the proximal nail fold, where it may be spread throughout three-fourths of the depth of the dermis.

Additional discussion with regard to dermal appendages, nervous tissue, and lymphatics may be found in the parent thesis.[3]

COMMENT

It is of interest that as early as the third month of fetal life, keratinized, loosely arranged lamellae of flattened cells, seen to evolve into the future mature nail may be observed to be developing from both the roof and the floor of the nail fold. At this stage, further invagination of the fold is still taking place. The eponychium shares in the keratogenic activity at this stage.

At 5 months, the future dorsal and intermediate nails may frequently be differentiated; the ventral nail, when present, makes its appearance shortly before term.

The mature nail unit may be shown by serial section with selected stains, especially silver protein, to be made up of three components, namely dorsal, intermediate and ventral. The silver protein-stain technique was originally selected to study nerve elements in the nail bed, but its ability to define the layers of the nail plate gave it additional value. Surprisingly enough, it also demonstrated the greatest histologic detail in the flattened cells of the nail substance.

In the past, it has been felt by many that the opacity of the lunula is a result of keratohyaline granulation. The findings of this study reveal that, in general, this area is free from keratohyalin-like granulation. If granulation is present, it is in minimal concentration. To the contrary, the granulation is heaviest in the epidermis of the roof of the nail fold and generative areas of the ventral nail hyponychium.

Many of these same authorities and most histologic texts state that the epidermis of the proximal portion of the nail bed in the region known as the matrix is thicker than other portions of the nail-bed epidermis. This was not evident in the specimens studied in the present investigation.

A changing pattern in the nail generative process at various stages of fetal existence and a dissimilar, variable pattern in the mature digit have led to the multiplicity of descriptions of the genetic phenomena to be found in the literature. In general, the dorsal and ventral nails arise through a process of macrocytosis, nucleolysis, and cell collapse, associated with granulation resembling keratohyalin. It is suggested that the process be called the inflation-deflation cycle. The intermediate-nail generative process could best be termed gradient parakeratosis because of the progressive broadening and flattening of the cells with prolonged retention of nuclei. Some nuclei remain in the nail unit and may be surrounded by vacuoles or eosinophilic material; for these, the term pertinax bodies is presented. Because they

tend to maintain the same depth throughout the length of the nail, it is felt that pathologic changes in the roseate nail bed will not be transmitted to the surface of the nail. Very fine granules are occasionally seen in the region of gradient parakeratosis, but they do not resemble the familiar keratohyaline granulation.

Figure 6 depicts the generative areas of the nail unit and hyponychium. The longitudinal diagram indicates that the dorsal nail may arise from an area which varies in size to a maximum occupying the proximal one-half of the roof and one-eighth of the floor of the nail fold. The generative area of the intermediate nail is seen to occupy the proximal nail bed. The area is limited by the distal margin of

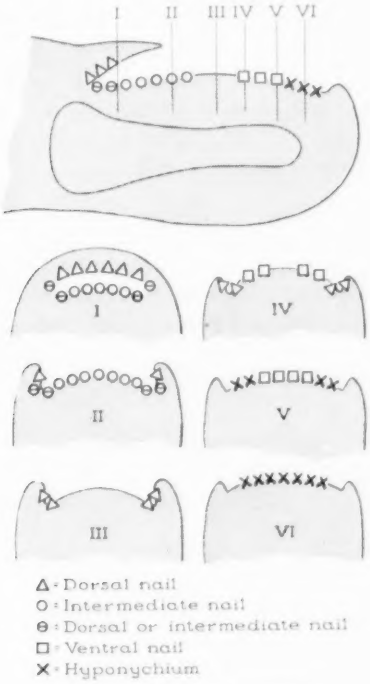

Fig. 6.—Sites of nail generation.

the lunula. This is the area familiarly known as the nail matrix. The term is improper if it is used to imply that nail generation is restricted to this site. Occasionally up to $\frac{1}{10}$ of the roof of the fold may give rise to intermediate nail. The ventral nail arises from a region occupying the distal one-half to two-thirds of the roseate nail bed. The hyponychium is seen to arise from the area overlying the distal prominence. This prominence is inconspicuous in the mature digit but is that portion of the nail bed immediately proximal to the anterior limiting furrow.

Cross Section I, through the proximal portion of the nail fold, depicts the generative area of the dorsal nail as encompassing the entire roof and frequently $\frac{1}{10}$ of the lateral region of the floor of the fold. The intermediate nail may arise from the lateral walls of the fold in this region as well as from the entire floor.

Cross Section II, through the lunula, suggests dorsal-nail generation from the lateral nail folds.

Cross Section III, through the midportion of the roseate nail bed, shows only the suggestive generation of dorsal nail from the lateral folds. Microscopic evidence of generation of intermediate nail from the roseate bed and lateral folds is equivocal. Generation of ventral nail might be found in some specimens when sectioned at this point.

Cross Section IV, through the distal one-third of the roseate bed, shows the bifurcated (fishtail) proximal portion of the generative region of the ventral nail. The proximal border of the ventral-nail generative area may be more gently curved so as to parallel the distal border of the lunula. The equivocal generation of dorsal nail from the lateral folds is seen.

Cross Section V, beyond the distal emergence, shows the centrally placed generative area of the ventral nail, no longer bifurcated, and the lateral formation of hyponychium.

Lastly, Cross Section VI, through the distal prominence, shows only generation of hyponychium.

SUMMARY

Highlights from original observations on the microscopic anatomy of the fetal and mature nail and surrounding soft tissue are presented.

In the past, histologic section of adult nail with nail bed has been so difficult as to be for the most part prohibitive. This investigation introduces a technique whereby the bony phalanx is mechanically removed, facilitating tissue preparation for microscopic examination.

The elimination of this major mechanical obstacle and the availability of numerous amputation specimens and fetuses led to the collection of a large series of normal digits; these were subjected to histologic review through a study of multiple microscopic sections.

In a study of serial sections from a fetal specimen the finding of a medium-sized blood vessel connecting the nail fold with the distal interphalangeal joint suggests the relationship between combined pathologic states of the joint and the nail.

Multiple sections and stains were of value in the interpretation of the various nail layers and their sites of origin. Up to the present time, all of the nail plate has been assumed to arise from the proximal nail bed (matrix). It is important to recognize that the most superficial layer of the nail may arise, at least in part, from the proximal nail wall. Thus one can explain changes in the surface of the nail seen as a result of alteration in the physiopathologic state of the paronychial tissue without concomitant change in the nail bed.

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INFRARED SPECTROSCOPIC STUDIES OF PIGMENTED SKIN TUMORS

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INFRARED spectroscopy has been successfully applied to a multitude of qualitative and quantitative analyses and investigations in the fields of chemistry and physics over a period of several years. Infrared spectroscopic studies in the fields of medicine and biology are of recent inception, by way of comparison. Pigmented skin tumors were examined in the infrared spectrometer during the course of this investigation, the objective of which was to study the infrared transmission and absorption of these lesions in the region of 2 to 16 μ. In succeeding paragraphs will be presented first an introduction to the subject of infrared spectroscopy, followed by an account of its use in the study of pigmented skin tumors.

INFRARED SPECTROSCOPY

The infrared spectrometer is a physical tool which is used for measuring and recording the infrared transmission and absorption of solids, liquids, and gases,[1] while the procedure itself is referred to as infrared spectroscopy. The infrared spectrum of a compound is a function of its chemical composition and results from selective absorption by the compound at certain frequencies in the infrared portion of the electromagnetic spectrum.* The infrared portion of the electromagnetic spectrum extends from about 0.75 μ to about 350 μ,[2] the range from 2 to 16 μ being most informative. Most organic compounds have a characteristic infrared spectrum [3] which is useful for identifying them, for differentiating them from similar substances, and for deducing information about their molecular structure.[4]

INFRARED SPECTROSCOPIC STUDIES OF PIGMENTED SKIN TUMORS

Materials and Methods.—Seborrheic keratosis, pigmented nevus, junction nevus, pigmented basal cell carcinoma, and malignant melanoma were the pigmented skin tumors selected for this investigation. A slice of tissue was removed from the central portion of each lesion immediately after excision and placed in the deep freeze. The remainder of the lesion was submitted for histopathologic examination. When slices

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* References 2 and 3.

from a sufficient number of lesions had been accumulated, they were trimmed of fat and lyophilized. The lyophilized specimens, averaging approximately 5 mg. in weight, were individually ground in a standard type of unglazed mortar and pestle by means of a mechanical laboratory stirrer attached to the pestle. In order to prevent excessive scattering of infrared radiation when the specimens were subsequently examined in the infrared spectrometer, it was necessary to grind each specimen for several hours. The yield was a fine powder, individual particles of which were small enough to pass a 300-mesh sieve. The powder was suspended in liquid petrolatum (Nujol) and examined in the micro position of a Baird double-beam recording infrared spectrometer using a sodium chloride prism.

Observations.—Several of the infrared spectrums obtained in the course of this investigation are reproduced in Figures 1 and 2. The spectrum of liquid petrolatum (Fig. 1*A*) is included for comparison with those of the pigmented skin tumors, since each of the powdered specimens was suspended in liquid petrolatum to facilitate examination in the infrared spectrometer. The significant absorption bands of liquid petrolatum, which occur at approximately 3.42, 6.84, and 7.23 μ (Fig. 1*A*) are encountered in all the spectrums shown but may be excluded from further consideration.

COMMENT

Although most organic compounds have a characteristic infrared spectrum, the agglomerations referred to as biological materials (including the pigmented skin tumors examined in this study) are so complex from a chemical standpoint that it is not feasible at present to attempt a complete and precise appraisal of their infrared spectrums. Data elicted in the course of this investigation permit the following comments, however, directed first to the infrared spectral region of 2 to 8 μ and next to the region of 8 to 16 μ.

The infrared spectrums of all the pigmented skin tumors are similar in the region of 2 to 8 μ (Figs. 1 and 2). An absorption band of equivocal import is present in most of the spectrums at approximately 3.1 μ (Figs. 1 and 2). It is believed that infrared absorption in the neighborhood of 3.0 and 3.4 μ is due to hydrogen stretching in relation to nitrogen or carbon, and that absorption bands for hydrogen stretching in conjunction with N-H occur between 2.9 and 3.3 μ.[5] Significant absorption bands occur at approximately 6.1 and 6.48 μ in most of the spectrums (Figs. 1 and 2), probably indicating the presence of carbonyl groups (C-O), which usually evoke the strongest absorption bands in the region of 5 to 7 μ,[6] and not infrequently the strongest in the entire infrared spectrum.[6] Randall and his associates[6] have found it expedient to include the following in the category of carbonyl groups: (*a*) carboxyl groups (acids, esters and carboxylate ions, including metallic salts and amino acid zwitter ions), (*b*) carboxyl derivatives (acid halides, nitrogen derivatives, thiolesters, lactones, lactams and anhydrides), and (*c*) other carbonyl groups (ketones, aldehydes, and the urea and cyclic diacylimide type of carbonyl groups).

The infrared spectrums of the pigmented skin tumors show dissimilarities in the region of 8 to 16 μ. Absorption zones of differing intensity are found between 8 and 11 μ in some of the spectrums (Figs. 1 and 2). It has been shown that the nucleic acids (ribonucleic acid, which is found in the nucleolus and cytoplasm of the cell,[7] and desoxyribonucleic acid, which is found in the chromatin of the cell nucleus[7]), are present in many highly cellular tissues in adequate concentration to cause sig-

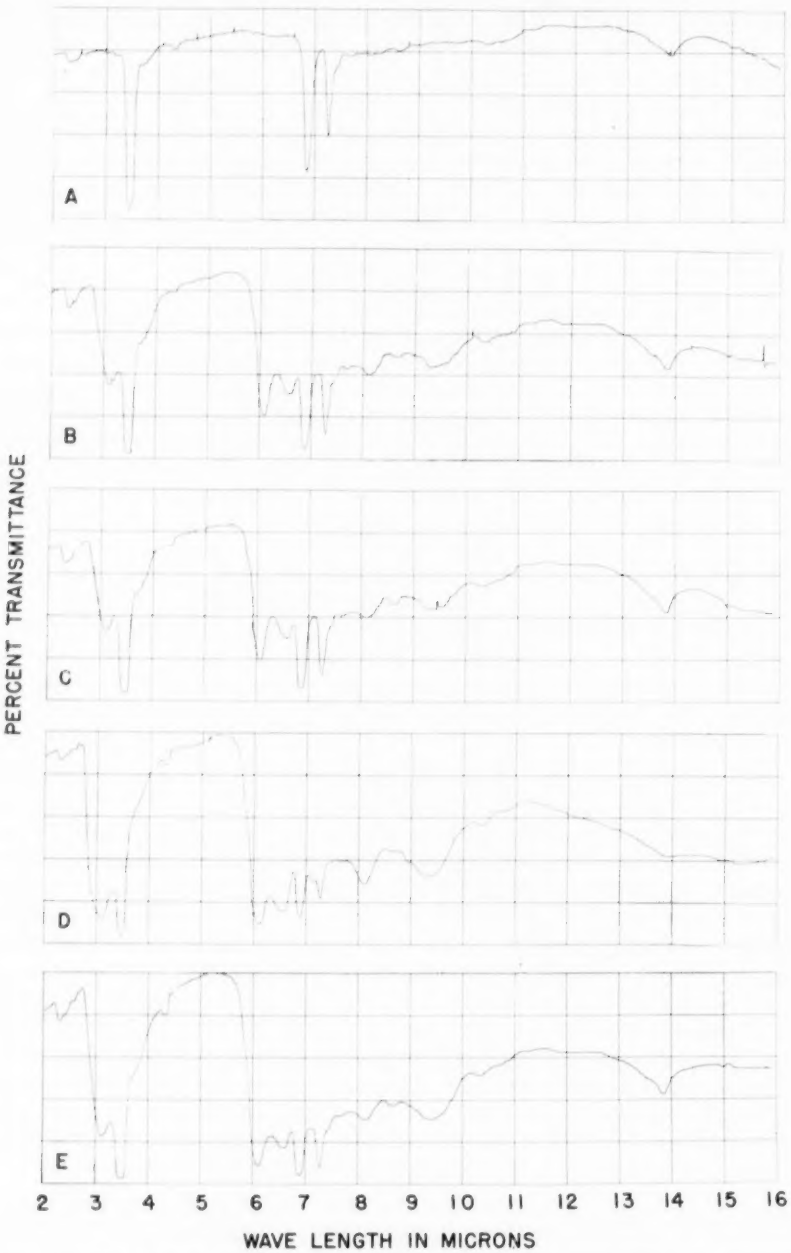

Fig. 1.—The infrared spectrums reproduced here were prepared from the following: *A*, liquid petrolatum; *B*, a primary cutaneous malignant melanoma of the face; *C*, a primary cutaneous malignant melanoma of the back; *D*, a metastatic lesion of malignant melanoma in the skin of the back; *E*, a metastatic lesion of malignant melanoma in the skin of the thigh. *B*, *C*, *D*, and *E* were prepared from specimens removed from four different patients.

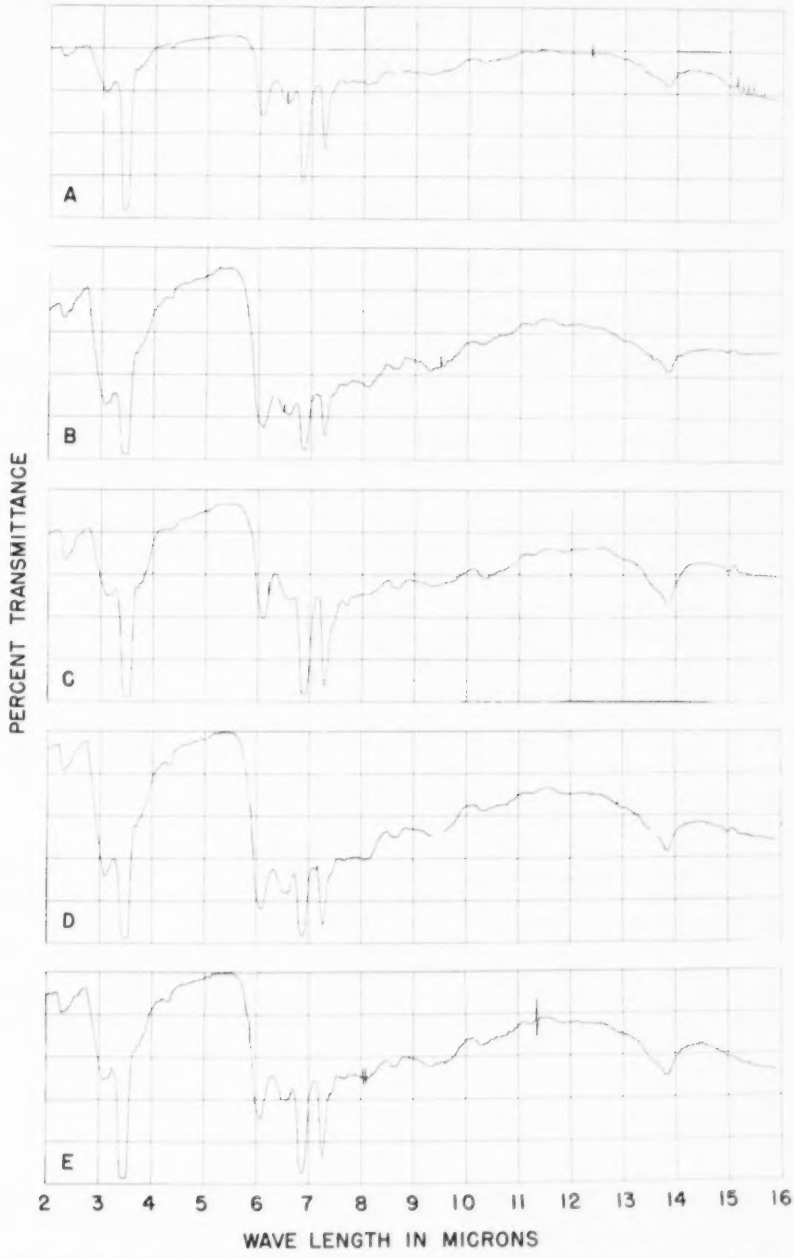

Fig. 2.—The infrared spectrums reproduced here were prepared from the following: *A*, a pigmented basal cell carcinoma of the back; *B*, a junction nevus of the sole; *C*, a pigmented nevus of the neck; *D*, a seborrheic keratosis of the abdomen; *E*, a pedunculated seborrheic keratosis of the axilla. *A*, *B*, *C*, *D*, and *E* were prepared from specimens removed from five different patients.

nificant absorption in the region of 8 to 11 μ, and that absorption intensities at 8.1, 9.3 and 10.3 μ can be correlated with the concentrations of nucleic acids in the tissue.[5] The nucleic acids are composed of phosphoric acid, pentoses, purines, and pyramidines, and the infrared absorption pattern of the nucleic acids is apparently due chiefly to the phosphoric acid and pentose constituents.[6] The 8 to 11 μ region of the infrared spectrums prepared from pigmented skin tumors (Figs. 1 and 2) indicates quantitative differences in nucleic acid content. In general it appears that malignant melanomas, both primary in the skin and metastatic to the skin, contain more of these compounds than other lesions examined.

SUMMARY

Pigmented skin tumors were examined in the infrared spectrometer, and the infrared transmission and absorption of these lesions in the region of 2 to 16 μ was studied. Although it was not possible to completely and precisely appraise the infrared spectrums of the pigmented skin tumors, because of inherent complexities in their chemical composition, several findings of interest were noted. The infrared spectrums of all the pigmented skin tumors were similar in the region of 2 to 8 μ, where there occurred significant infrared absorption bands at approximately 6.1 and 6.48 μ, probably indicating the presence of carbonyl groups. The infrared spectrums of the pigmented skin tumors showed dissimilarities in the region of 8 to 16 μ. Absorption zones of differing intensity were found between 8 and 11 μ in some of the spectrums. It appears that nucleic acids are present in many highly cellular tissues in adequate concentration to cause significant infrared absorption in the region of 8 to 11 μ and that malignant melanomas contain more of these compounds than other lesions examined in the course of this investigation.

ABSTRACT OF DISCUSSION

Dr. John R. Haserick, Cleveland: Drs. Cawley, Rathbun, and Wheeler, in this excellent presentation, have presented a method which is new to dermatopathology and which is so complex as to be beyond the scope of even the well-equipped laboratories of general pathology.

Most of us are not familiar with the techniques of tissue analysis by radiation. We are more at home with the other histochemical procedures, for example, the chemical reactions on tissues, such as the PAS staining for mucopolysaccharides or the Sudan stain for fat, the enzyme-staining methods as for alkaline phosphatase, or the microincineration technics.

Radiation analysis has been done in other fields, as Dr. Cawley pointed out, and only recently has been employed in medical research. The absorption spectrum of ultraviolet light has been used by Klemperer and his group in the analysis of the nucleoproteins of lupus erythematosus. Fluorescence microscopy has been used for the analysis of vitamin A and as Dr. Brunsting has stated, for the porphyrin studies as done by Watson, Schmidt and Schwartz.

While these procedures are of unquestioned value, the pitfalls are always the same. The complexity of the tissue and of the method may lead into an erroneous interpretation of the absorption spectrum in question. We are reminded of the time-honored method of radiation analysis used today in general pathology, namely, the Nicol prism technic for the identification of cholesterol. These prisms, as you know, polarize the light, and the birefringence of the cholesterol crystals supposedly permits their identification. We know now that birefringence is a quality of crystals in general rather than of any particular crystal such as cholesterol, and other means of identification must be employed to come to the final analysis.

While this is obviously an oversimplified analogy, it points up the major defect of radiation analysis, namely that things may not be as they seem. Therefore, while we are assured of the quality of this work by our acquaintance with these investigators, we must await their further efforts before the true worth is evaluated.

DR. FRANCIS A. ELLIS, Baltimore: Dr. Cawley gave, as he always does, a beautiful presentation. There is one question I want to ask. What were the spectrum curves on normal tissue and on inflammatory tissue? I don't believe these were shown.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I should like to ask Dr. Cawley whether the method of infrared spectroscopy has been applied to the blood of patients with systemic lupus erythematosus in order to detect the presence of altered desoxyribonucleic acid.

DR. EDWARD P. CAWLEY, Charlottesville, Va.: Although infrared spectroscopic studies in the field of medicine are of recent inception, the method appears to hold great promise for the future. In answer to Dr. Ellis' question, we have concentrated our efforts on infrared spectroscopic studies of pigmented skin tumors and fungi and have not investigated normal and inflammatory tissue with this tool. Woernley's paper,[5] however, presents the infrared spectrums of a number of normal tissues. In answer to Dr. Brunsting's question; Woernley,[5] and Blout and Mellors (Blout, E. R., and Mellors, R. C.: Infrared Spectra of Tissues, *Science* **110**:137 [Aug. 5] 1949) have published infrared spectrums prepared from blood, but infrared spectroscopy has not been applied to the blood of patients with systemic lupus erythematosus, to the best of my knowledge. Such a study might prove both interesting and profitable.

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DERMABRASION OF THE ACNE PIT

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HISTORY

PIT, SCAR, and blemish have since antiquity been the bane of patient and physician. The oldest medical document extant prescribed an abrasive "to make the face smooth" (Papyrus Ebers, 1,500 B. C.):

Water from the qebu plant
Meal of alabaster *
Fresh Abt grain
Sig: Mix in honey, make into a pap, mix in human milk and anoint the face therewith.

Thirty-four centuries later finds this prescription still in use with but minor changes (Unna, 1900 A. D.):

Cremor gelanthi
Sapon
Pulv. pumicis *

* Note the similar abrasive materials.

In relatively recent times, the following methods have been advocated for the removal of pits, tattoos, scars, pigmentations (including chloasma), milia, ephelides, lentigines, nevi, verrucae, seborrheic keratoses, keloids, furuncles, wrinkles, rhinophyma, and "enlarged pores." Some workers have published the details of various methods; the work of others is known to us personally.

1. Acupuncture (Needling)
   Variot (1888)—Tattoos (10% tannic acid followed by silver nitrate)
   Brault (1895)—Tattoos (zinc chloride)
2. Scarification (Multiple Incisions)
   Rossignol (1881)—Acne, rhinophyma, nevus flammeus
   Karpelis (1937)—Tattoos (followed by potassium permanganate)
   Cannon (1940)—Acne pits, rosacea
   Eller and Wolff (1941)—Acne pits and scars
   Lerner (1948)—Tattoos (tannic acid and silver nitrate)

Read before the Seventy-Fourth Annual Meeting of the American Dermatological Association, Inc., White Sulphur Springs, W. Va., April 16, 1954.

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of the University Hospital.

3. Electrodesiccation
   Kromayer (1905)—Acne scars
   Miller (1908)—Tattoos
   Gourvich (1935)—Smallpox scars
   Ibarra (1943)—Rhinophyma
   Hartman (1952)—Acne scars
4. Surgical Excision and Surgical Shaving
   Kromayer (1905)—Tattoos, pigmentations, scars, abscesses, comedones, hypertrichosis, nevi (punch with cylindrical knife—motor-powered tool)
   Miller (1925)—Scars
   Gourvich (1935)—Scars
   Chaton (1937)—Tattoos
   Sheehan and Swanker (1950)—Acne scars
   Lowenthal (1953)—Smallpox scars (punch—autograft—electrodesiccation)
   Orentreich (1953)—Deep acne pits (punch—autograft—abrasion)
5. Chemical Caustics
   Cannon (1940)—Acne pits (trichloroacetic acid)
   Winter (1950)—Freckles (phenol in ether)
   MacKee and Karp (1952)—Acne scars (phenol)
   Cohen (1953)—Freckles (solid carbon dioxide)
6. Cryotherapy with Carbon Dioxide Slush (Carbon Dioxide, Sulfur and Acetone)
   Giraudeau (1928)—Active acne
   Karp, Nieman, Lerner (1929)—Acne scars
   Dobes and Keil (1940)—Acne scars
   Hollander and Shelton (1941)—Acne scars
   Friedlander (1942)—Acne scars
   Zugerman (1946)—Acne scars
7. Abrasion
   Kromayer (1905)—Keratoses, pigmentations, acne scars (dental burrs and rasps—hand and motor-powered tools)
   Stein (1928)—Kromayer's methods
   Shie (1928)—Tattoos (dental drill)
   Jason (1935)—Tattoos (bristle and wire brushes—hand-powered tool)
   Iverson (1947)—Tattoos (sandpaper—hand-powered tool)
   McEvitt (1948)—Acne pits (sandpaper—hand and motor-powered tools)
   Schreus (1950)—Keratoses, tattoos and pigmentations (grinding discs—motor-powered tool)
   Barker (1951)—Acne scars (sandpaper)
   Rosenberg (1952)—Tattoos (sandpaper)
   Strakosch (1953)—Tattoos (sandpaper)
   Blackledge (1953)—Acne pits (sandpaper)
8. Dermabrasion with Ethyl Chloride—Wire Brush—Motor-Powered Tool
   Kurtin (1952)—Acne pits, tattoos, wrinkles, etc.
   Wexler (1952)—Acne pits, rhinophyma
   Orentreich (1953)—Acne pits and nevus flammeus
   Kimmelman (1953)—Acne pits
   Monash and Rivera (1953)—Acne pits
   Grupper (1953)—Acne pits
   Rattner (1954)—Acne pits
   Eller and Lubowe (1954)—Acne pits
   Le Van (1954)—Acne pits
   Hubler (1954)—Acne pits

DERMABRASION

Modern Evolution.—Kromayer, if anyone at all, founded modern cosmetic surgery in the dermatologic sense. For 30 years, he devoted much time, effort, and ingenuity to procedures and instruments of his own devising. After a period of

observation in dental clinics, he adapted motor-powered tools to dermatologic surgery, and in 1905 he first wrote on his *Rotationsinstrumente*. Cylindrical knives (*Zylindermesser*) of diameters 0.8 to 10.0 mm. were powered by ordinary dental motors and applied vertically to the skin to remove lesions of various sizes. This procedure he called *Stanzen* (punching), and it ever remained Kromayer's favorite therapeutic method in the treatment of various conditions, including tattoos, pigmentations, scars, abscesses, nevi, and hypertrichosis. With infinite patience, he punched 300 comedones from one patient, 200 hairs from another. Very fine borers were also effectively used for drilling out follicular contents. Sometimes he excised strips by using the rotating knives horizontally to the skin, while on other occasions he employed steel burrs and rasps for the abrasion of lentigines, freckles, warts, and pigmentations. He also noted that ethyl chloride could be used as an anesthetic and skin hardener. However, he felt that the actual pain was of such insignificance that ethyl chloride only prolonged the surgical procedures needlessly.

In the second edition (1929) of his small text, Kromayer first speaks of a "leveling operation" for smallpox scars. The healthy skin between the pocks was abraded down level with the floor of the pit. For this, he found all anesthetics unsatisfactory except "nerve" anesthesia.

In 1933, Kromayer published another paper on abrasion with steel burrs. Herein he cautions that only "planing" limited to the epidermis and cutis vasculosa will heal without scarring, and he therefore employed it only for superficial conditions like juvenile warts, freckles, and pigmentations. No anesthesia was used or required.

Finally, in 1935, Kromayer was back to his rotating round knife with which he punched out 100 coal particles that had become embedded in a patient's face. One year after this operation, there was no noticeable scarring.

Iverson (1947) first used carpenters' sandpaper, grit 0 and 00, wrapped around a 3-in. (7 cm.) roll of gauze bandage for the removal of traumatic tattoos of the face, with spectacular results. The operation, under general anesthesia, was combined with the coagulating action of tannic acid and silver nitrate. To date, he has reported no untoward developments. He fully realized the fear factor in the operator and stressed this point:

> There will be a natural tendency at first to be timorous about carrying the procedure too deep. But it should be kept in mind that the dermal layers are composed of a very compact arrangement of elastic fibers and other connective tissue elements, and so are capable of tolerating an inordinate amount of abrasion, and their regenerating powers are exceedingly active. We have found it safe to carry the procedure, if necessary, to the point where subcutaneous tissue gradually makes its appearance in pinpoint elevations of fat through the abraded corium.‡ Large areas of subcutaneous tissue will not appear suddenly. In only two instances have we taken the procedure to the point where after healing, there was evidence of scar. These scars were not extensive and were easily corrected by simple excision and primary closure.

McEvitt (1948) was the first to apply the sandpaper technique to the correction of acne pits. With the patient under general anesthesia, he abraded the entire face by hand, and also used assorted motor-driven discs for small inaccessible facial contours. An average of three sandings per patient was required.

‡ This is apparently the zone where corium and subcutaneous fat intermingle. For a conception of this depth see Table.

The first report on sanding to appear in a dermatological journal was by Rosenberg (1952), who removed an accidental tattoo from the face with sandpaper, grit 000. One year later, there was no evidence of residual cicatrization.

Strakosch (1953) sandpapered a tattoo of the forearm, with excellent cosmetic results and a fine residual scar. Generalized freckles of the face in a young redheaded woman also responded well to this method.

Kurtin § (1952) presented a method of refrigeration-abrasion, "Skin Planing," at a meeting of the Dermatological Section, Mt. Sinai Hospital, New York. By freezing large areas of skin with ethyl chloride, Kurtin fouund that there was no need for general anesthesia. It therefore became possible to use this technique as an office procedure rather than under hospitalized conditions as previously required. In addition, this provided a rigid dehematized surface so that abrasion was thus made simple, safe, and relatively free of hemorrhage. Instead of using sanding discs or steel burrs, he devised a motor-powered wire brush for the abrading process. In his report, Kurtin (1953) discusses the results obtained in the treatment of acne pits, traumatic scars, tattoos, wrinkles, and other conditions. He found that patients with acne scars required an average of three treatments to obtain satisfactory results.

Wexler || (1952) has had considerable experience with "skin planing" in the treatment of acne pits and claims excellent results. He has also applied this method satisfactorily for the correction of rhinophyma.

Kimmelman ¶ (1953) has also treated acne pits with the technique described by Kurtin and is satisfied with the results.

Lowenthal (1953) revived the punch method for pockmarks and observed that the use of a 2 mm. punch did not leave a visible scar. His excellent paper describes the transplanting of punched discs of skin as grafts to fill in biopsy sites. Where the transplant is in excess, Lowenthal uses electrodesiccation for leveling.

Orentreich # (1953) has combined several procedures for the treatment of solitary deep pits and other local lesions. These lesions are punched out, a punch graft is inserted and after healing, the area is abraded for leveling.

Pit Problem—Mechanics of Dermabrasion.—The acne pit is a scar in and around the pilosebaceous unit. Since these units normally are situated at various depths in the dermis, it is obvious that the pits also can descend to varying levels.

The older methods employing acupuncture, incision, scarification, electrodesiccation, leveling, chemical caustics, and cryotherapy produced cosmetic improvement by making the actual scars wider and shallower. The pit floor, however, remained in its fixed position.

If the pit, including the rim, walls, and floor, could be satisfactorily and safely removed in its entirety, a solution to this "hopeless disfigurement" (McEvitt) would be at hand. By excision of strips of skin, including dermis, one can remove groups of pilosebaceous units and accompanying pits. Furthermore, the deeper one cuts through the dermis, the more is removed. This method is the well-known Ollier-Thiersch, or split-skin, graft and could well be called dermal excision.

§ Kurtin, A.: Paper read at the meeting of the Dermatological Section, Mt. Sinai Hospital, New York, January, 1952.

|| Wexler, L.: Personal communication to the authors.

¶ Kimmelman, J.: Personal communication to the authors.

Orentreich, N.: Personal communication to the authors.

By analogy, if an abrasive is substituted for the scalpel and if the abrasion is deep enough, it should remove similar numbers of pits and pilosebaceous units which would then actually be stripped out by the abrading instrument. This method we have called dermabrasion. The deeper the abrasion, the more of the dermis is removed and the more acne pits and pilosebaceous units with it.

The Histology and Healing of Dermabrasion.—The literature on the histology of the acne pit is meager, since the skin on the face is a "hands-off" biopsy area. However, from recent studies on the healing of Ollier-Thiersch-graft donor sites and other observations, a valid series of conclusions can be drawn and applied to the healing and possible future outcome of the facial skin following dermabrasion.

Before elaborating upon these points, attention is drawn to the accompanying table of some physical dimensions of the skin in order to provide an orientation for the subsequent discussion.

It will be recalled that Iverson (1947) carried his sandpaper abrasion to the level of the subcutaneous fat, and when he kept the abrasion superficial to this region his treatment sites healed without visible scarring. Rosenberg (1952), in describing the histology of a facial tattoo that was also subsequently abraded with

Thickness of Epidermis and Its Layers; Corium and Its Parts and Entire Skin *

Part	Range of Values for Most of Skin, Mm.	Average, Mm.
Epidermis	0.07-0.17	0.12
Stratum corneum	0.04-0.05	....
Stratum mucosum	0.07-0.08	....
Corium	1.7 -2.0	1.8
Pars papillaris	0.05-0.2	....
Pars reticularis	1.5 -1.8	....
Hypoderm	0.08	0.08
Entire skin	2.0 -2.2	2.0

* After Leider and Buncke

sandpaper, states "in the mid-corium and extending from the subpapillary layer to the level of the sweat glands, there were circumscribed masses of cellular infiltrate. Each of these inclosed considerable dark pigment of a yellow to brownish-black hue." His photomicrograph of the healed areas that followed successful abrasion shows ample sebaceous structures at this lower one-third of the dermis. Abrasion removed the pigment completely, and the treated areas healed without scar. These reports demonstrate that, on the face at least, one can abrade down to sweat gland level and not produce scarring.

Brown and McDowell (1943) in their text discuss the histology of healing of the Ollier-Thiersch graft. They prefer the term "splint-skin graft," and they note its resemblance to a deep abrasion. They have taken as many as five grafts from one area, with the second crop removed just 19 days after the first. Donor sites heal from the deep glandular epithelium which covers the surface in six days, and by the ninth day healing is complete and keratin is being shed. They also write, "Grafts will grow hair, sweat and secrete sebum. . . . The cutting (of grafts) may sound difficult, but actually it is fairly easy and nearly all interns and residents going through the service are able to obtain good grafts after just a few trials."

Gillman, Penn, Bronks, and Roux (1953) have recently published an excellent and detailed monograph dealing with the healing and grafting of wounds. They

analyzed the histogenesis of healing of a Thiersch-graft donor site by doing repeated biopsies up to 80 days postoperatively. The donor site was the anteromedial aspect of the middle third of the arm and the site measured 6 by 4 in. (15 by 10 cm.). The authors' description dealing with the histogenesis of the healing process is elaborate, but it is quoted in some detail because it is so important:

Blood shed at the time of removing the graft clots on the surface, is rapidly organised into fresh granulation tissue; epithelium generated from the neighbouring undamaged skin and from the hair follicles and sebaceous gland ducts covers the surface of these granulations within six to ten days; this actively growing epithelium is apparently stimulated to invade the granulations, forming "pseudo" rete pegs; the epithelial spurs which invade the granulations frequently become separated from the surface epithelium, become surrounded by lymphocytes, histiocytes and fibrocytes, and are ultimately treated as foreign bodies. These isolated epithelial islands may undergo internal keratinisation to form epithelial pearls, which elicit foreign body reactions. It was found, in spontaneously healing Thiersch donor sites, that the epithelium lining the ducts of sweat glands does not grow so vigorously as that lining the hair follicles and sebaceous gland ducts. These sweat ducts encounter difficulty in penetrating the fresh granulations. . . . The new epithelium, which covers the site of injury, does not regain the detailed morphological appearance of the original skin of the area; for many months, and even years, the junction of the epithelium with the dermis seems abnormal; the new dermal tissue developed within the granulations retains a different pattern or organisation of fibers and blood supply from that of the untraumatised neighbouring skin of the area. The final appearances of the healed Thiersch donor site resemble, but are not identical with, those of a scar. The untreated healed Thiersch donor site can be distinguished from normal skin of the area even eight years after removal of the graft.

Earlier in the article the authors state that

it is now common experience, since the use of split-skin grafts has become widely adopted as a therapeutic measure, that, provided the graft is not taken from too great a depth into the dermis, the entire donor site will become completely epithelialised and will apparently heal within a remarkably short time without "true" scar formation. So much so, that it is practice of many surgeons in this field to work to harvest from the same area as many as six crops of skin with as little as three weeks' interval between each harvesting (Brown and McDowell, 1949; Medawar, 1945*b*). Despite this extensive trauma, the skin of the donor area apparently recovers completely and without any residual scarring.

Elsewhere the authors report that "daily observations in surgical and casualty wards show that extensive superficial abrasions almost invariably heal without scar formation, except in keloid-susceptible individuals." Eight years later, a Thiersch-graft donor site on "examination with a hand-lens usually reveals fewer hair follicles and sweat-gland orifices than in a similar area of the immediately abutting normal skin."

the major source of epithelium covering the denuded area in these experiments seemed to be generated by the surrounding healthy skin. However, the sebaceous glands and hair follicles also play some part and contribute an indeterminable quantity of epithelial cells to cover the raw areas. The epithelium lining the hair follicles and sebaceous glands grows vigorously and by the ninth day . . . many of the sebaceous glands have already grown through the granulations covering the raw surface and have opened to the surface.

From the histopathologic point of view, dermabrasion, whether accomplished by rasps, sandpaper, or motor-driven wire brushes, is similar to the surgically performed Ollier-Thiersch split-skin graft. If, as stated by Brown and McDowell, the cutting of skin grafts is easy, certainly dermabrasion is far less difficult. Furthermore, the treatment of the acne pit on the skin of the face gives the physician a regional advantage as demonstrated by earlier reports. Rosenberg, after the suc-

cessful abrasion of a tattoo on the face, was able to demonstrate by histologic examination the complete regeneration of epithelium without scarring. In contrast, Strakosch, employing a similar abrasive technique for the removal of a tattoo on the forearm, demonstrated clinical evidence of scarring. It is, therefore, apparent that the face is a unique area for the application of dermabrasion. As the facial skin is richly seeded with pilosebaceous units, reepithelization is rapid and healing takes place without clinical scarring. This is in agreement with Kurtin's statement that "at no times does the healed skin have the glazed firm appearance of scar tissue."

Since dermabrasion removes pilosebaceous units from the skin and since this unit is the pathological locus in acne vulgaris, the method could be applied to the treatment of an active acne process. This is demonstrated by the following observation:

In many instances patients were subjected to dermabrasion during an exacerbation of the acne. It was of special interest that after the abrasion there was excellent healing of the acne process. In those in whom there was a subsequent exacerbation of the acne, it was more or less limited to the untreated areas.

The appearance of milia is to be expected in the treated areas. These lesions are epithelial cysts filled with keratin. They are produced when tongues of cells are cut off from the regenerating epidermis and come to lie free in the dermis. When they do occur, they offer no problem and are easily expressed.

Clearly, many types of skin lesions may be removed by abrasion. Whether this is accomplished by knife, curette, desiccator, x-ray, caustic, sandpaper, or wire brush is purely an individual preference. A long list of conditions is, therefore, hardly necessary here. If one completely abrades a lesion in the equivalent area and depth that one uses a knife to excise it entirely, one has accomplished the same purpose. When a lesion is removed from the face, no visible scar should result, provided the lesion does not descend to the subcutis.

RESULTS

Late in 1952, we began using the refrigeration-abrasion method for the ablation of acne pits and to date have treated a series of 420 patients. Even though all persons can be helped, selection for this therapy is still of utmost importance. Deep, narrow, "ice-pick" pits are particularly difficult, as are the undulating, irregular, wavy type of scars. In spite of these difficult types, no patient should be discouraged, since from the nature and mechanics of the procedure some improvement can be granted to almost every case. As in all contemplated medical work, some assessment of the patient's mental state should be made. The pit and the preceding or attending acne process are especially prone to leave some distortion of the psyche. The bizarre thinking, feeling, and acting of some of these patients are all too familiar to the dermatologist. It is, therefore, imperative that the physician be patient and sympathetic in his explanations and avoid exaggerated claims. His kindness will be amply rewarded by the patients' often ecstatic reaction to some of the excellent treatment results.

We, too, feel that ethyl chloride is the refrigerant-anesthetic of choice. In addition to its local effect, it is also quite probable that the freezing produces some

degree of superficial necrosis. Although any type of abrasive tool may be used, the steel wire brush seems preferable. Solid steel burrs have proved unsatisfactory and even hazardous.

After the abrading procedure has been completed, petrolatum gauze is applied and the face is then dressed. The ointment has one purpose, namely, to facilitate the removal of the dressing. All dressings are removed in 4 to 24 hours by the patient and the treated areas allowed to air-dry. No other dressing is permitted. The sooner the abraded area is covered by a dry crust, the sooner the patient will be comfortable. Any interference with this drying only delays healing. In many instances, especially after retreatment, the patients remove the dressing as soon as they return home. The use of antibiotics as a postoperative dressing has been discontinued as unnecessary. The wounds do not become infected in the presence of reasonably good personal hygiene and normal skin resistance. Since epithelization is complete in six to eight days, patients are instructed to soak off the adherent dry crust with warm water on the eighth day. Thereafter, soap washings, acne medications, and cosmetics are permitted, while men may also resume shaving at this time.

The number of retreatments will depend on the type and depth of scars as well as the depth to which the physician goes with his abrasion. Since we attempt to go rather deeply, our results are satisfactory even after one thorough abrasion. In only rare instances have we repeated the procedure more than three times. Many of our patients have been followed for 30 months, and to date we have observed no evidence of postoperative infection or keloid. It is of special interest that many of these patients have had varying amounts of superficial x-ray therapy administered from months to years prior to dermabrasion. There has been no evidence of untoward end-results or any delay of the healing time in such persons.

In order to give a smooth and even appearance, the entire face, including nose, chin, and forehead, when indicated, is abraded. If the abrasion is blended into the temples, nasolabial folds, and jaw angles, there will be a minimal demarcation of the treated areas. Occasionally, there may be a persistent erythema or the development of a slight hyperpigmentation in the treated areas. It has been noted that both will fade within a relatively short time without intervention.

After reepithelization, the facial skin is still heavily seeded with pilosebaceous units, and so there should be no concern as to the possible development of premature drying and wrinkling.

In order to obtain opinions of others, a questionnaire was sent to physicians who have had experience with this procedure. According to the responses received, a total of 2,206 cases had been followed for a sufficient period of time for evaluation. With very few exceptions, the results were extremely satisfactory. Some physicians who had used other types of abrasion procedures felt that the end-results were better with this particular technique.

It is our opinion that in those instances in which the anticipated good results were not obtained, it was due to poor selection of patients or the failure to abrade to a sufficient depth.

We are in complete agreement with McEvitt (1950), who states: "No case has come to my attention in which some degree of improvement has not been

achieved, and in most instances, the improvement has been considerable. It is hoped that the use of these methods will become more widespread for the benefit of afflicted persons."

This opinion is corroborated by Blackledge (1953), who soundly takes the medical profession to task for its stubborn unwillingness to understand fully the value of dermabrasion and to recommend its more frequent use. He writes:

"There has been nothing developed to date in the field of medicine or surgery which closely approximates the beneficial effects of the abrasion treatment for superficial scarring of the skin by such diseases as acne and smallpox."

SUMMARY

A review of the history, mechanics, and histology of dermabrasion is presented.

Dermabrasion is the method of choice for the treatment of the acne pit. Failure of improvement is due solely to the superficiality of the abrasion and the timidity of the physician.

Each successive abrasion should give additional improvement, since more pits are stripped.

The skin of the face will heal without clinical scar, provided the abrasion is limited to the levels discussed.

The following physicians contributed case studies to this report:

Baer, T. W.	Keen, R.	Robbins, S.
Behrman, H. T.	Kimmelman, J.	Roberts, D. P.
Belisario, J. C.	Larralde, J.	Robinson, M.
Bereston, E. S.	Leider, M.	Robinson, R. C. V.
Bloom, M.	LeVan, P.	Rogin, J. R.
Edelson, E.	London, I. D.	Schwartz, O.
Eller, J. J.	Loveman, A.	Shiller, A.
Fisher, A. A.	Lubowe, I.	Sloane, M.
Fliegelman, M. T.	Mopper, C.	Stolar, R.
Franks, A.	Mochella, S. L.	Weidman, A. I.
Glick, H. V.	Niedelman, M. L.	Weiner, M.
Goldberg, L.	Nordstrom, R. C.	Werzman, J.
Goldfarb, N.	Orentreich, N.	Wexler, L.
Grekin, J.	Quero, R.	Wortzel, M.
Gross, E.	Rattner, H.	Wright, C. S.

ABSTRACT OF DISCUSSION

Dr. Carroll S. Wright, Philadelphia: Frankly, it was with considerable fear, trepidation, and hesitation that Dr. Elmer Gross and I decided to employ this refrigeration-abrasive method for the removal of acne scars in our private office. The results of the few cases that I had seen after treatment by a Philadelphia authority on sandpapering, whose name is quite well known to you, had been disappointing. Furthermore, the cost had proved prohibitive to many patients who had considered having the sandpaper abrasion. Unfortunately, at least in Philadelphia, the majority of the persons with severe scarring are in the low-income bracket, clerks, stenographers, and others, who cannot afford some of these more expensive procedures. I do not intend to suggest fees that must vary at times, but we felt that we could do each planing for approximately a third to a fourth of the cost of the sandpaper abrasion, which, as you all know, must include hospital costs and nursing care.

I worried about giving up office space, but that has been temporarily solved by doing these planings out of regular hours.

More than 20 years ago, Dr. Jay Frank Schamberg brought back from Europe the Kromayer apparatus for the treatment of scars. It was never used in our office, either by Dr. Scham-

berg or by me, as we were uncertain of the exact technique. In fact, it was put back in the cabinet, where it rests to this day, and Dr. Schamberg continued to use the phenol-cresol applications which he had used for many years for the treatment of scars.

We do not promise these patients complete eradication of scars. I may say that it has always been a source of great pain to me to have to tell patients that we can probably help their acne but their scars will persist. Today, every patient we have treated has been pleased with the improvement. Most important is the mental "lift" that seems to follow even the moderate lessening of the scarring. To date, we have had no complaints about the results and no undesirable sequelae. I may say that two patients showed a sort of chloasma-like pigmentation for a while. This was probably the result of the inflammatory reaction, and it disappeared uneventfully.

Every patient treated has improved in appearance, although it must be admitted that deep scars do not entirely disappear even after two abrasions, which is the most any of our patients have received to date.

I have advocated conservatism as regards the depth of the abrasion, fearing that a few of the treated cases might show a tendency toward keloid formation, but we have not seen the slightest evidence of keloid or even hypertrophic scarring in our 87 cases.

I wish to congratulate Drs. Rein and Blau on their excellent review of the entire subject of the treatment of acne scars and for definitely stating that dermal abrasion is the method of choice in the treatment of the acne pit. This I firmly believe from my limited experience.

DR. JOSEPH J. ELLER, New York: I have been actively interested for more than 20 years in the removal of pitted and traumatic scars, and I have used various methods such as scarification, electrodesiccation, the so-called sandpaper surgery, carbon dioxide snow, trichloroacetic acid and phenol.

Of all these, the sandpaper method was the best, but it has disadvantages, such as hospitalization and the possibility of silica granuloma caused by small imbedded particles.

For more than three years now I have used the refrigeration-abrasion-rotary steel brush method and have found it superior and much more satisfactory than any of the previously mentioned methods.

In an article published in the April 15, 1954, issue of the *New York State Journal of Medicine*, I reported the results of more than 200 cases of various types of scars, with illustrations showing the results of this form of therapy.

I have also collected the results in another group of cases, such as "fixed freckles," senile lentigenes, chloasma, and lupus erythematosus lesions, the results of which will be reported in another paper. (A group of lantern slides were shown illustrating the results of dermabrasion.)

I wish to congratulate Drs. Rein and Blau for the excellent presentation they have given us here today. They gave a splendid review of the literature pertaining to the various abrasive methods, and their discussion of the histopathology was excellent.

DR. CHARLES R. REIN, New York: I wish to thank Drs. Eller and Wright for their discussion. The use of abrasion techniques has been such a controversial question that I had expected a more extensive discussion of the problem at this time.

Our patients have been followed for as long as three years, and the treated areas appear to improve with time. This is in contrast to the results obtained with phenol applications, wherein some of the apparent improvement is due to edema and the scars become more noticeable again several months after the treatment when the edema subsides.

We have not used, nor do we advocate, this procedure for the treatment of active acne as mentioned by Dr. Eller. It is of interest, however, that in treated patients who may develop an exacerbation of the acne months after dermabrasion, the new lesions appear much less frequently in the abraded as compared with the nonabraded areas.

One patient with extensive scarring due to lupus erythematosus has been treated with good results. A second patient with xeroderma pigmentosum was also subjected to dermabrasion. Some nine months later, the abraded areas were covered with normal-appearing skin, and there was minimal recurrence of islands of hyperpigmentation.

A few points that Dr. Blau and I should like to stress are these:

1. Do not promise the patient too much and, if possible, underestimate the end-result.

2. Be careful in the selection of the patient as to the psychological status and the type of scarring.

3. Take black and white photographs of all patients prior to therapy. Post-therapeutic pictures are not necessary.

4. Remove the dressings as soon as possible after dermabrasion.

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GROUP PSYCHOTHERAPY IN ADULT ATOPIC ECZEMA

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THIS STUDY grew out of a psychiatric appraisal of a group of 30 adult atopic eczema patients previously reported.[1] That project has been extended to include over 50 subjects and is still in progress. It was understood from the beginning that this is no novel approach to the problem. Numerous dermatologists, psychiatrists, and allergists * have asked and attempted to answer questions about the psychological aspects of this disease, and psychotherapy has been previously used in its management.†

The dermatologist in this study has been singularly impressed by the similarity in behavior and demeanor of the atopic eczema patients encountered in private and clinic practice. The psychiatrists, too, after studying a fair number of them were struck by the fact that they had personality and character traits in common to a point that was significant—considering that they were selected only on the basis of having the same cutaneous disorder. It was found that they had primitive personality structures, and various immature character traits were demonstrable. They showed crippling inhibition of their aggressive and erotic drives, and depression was very prominent in their emotional make-up. Repeatedly there had been an unhealthy child-parent relationship in their lives, with parenteral rejection often strikingly evident. Invariably, exacerbations of their eczema in adult life could be correlated with stressful situations, not catastrophes but rather the usual accompaniments of normal maturation.

In the previous study, psychotherapeutic implications were considered briefly, and certain positive impressions were gained. It was concluded that atopic eczema patients were generally not suited for insight-producing or depth psychotherapy. They seemed to need techniques which were more superficial, which provided emotional support and encouragement, with occasional active intervention by someone

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Social Studies in this series were done by Mary Mally, M.S.S., and psychological testing was under the supervision of Anne M. Ritter, Ph.D., both of the Staunton Clinic and University of Pittsburgh.

From the Department of Dermatology and Syphilology (Dr. Guy), and from the Department of Psychiatry, Instructor of Psychiatry (Dr. Shoemaker), and Staunton Associate Professor of Psychiatry (Dr. McLaughlin), School of Medicine, University of Pittsburgh.

* References 2 through 9.

† References 10 and 11.

into the situational tangles in which these people are so apt to get themselves enmeshed. It was felt that such measures could be carried out by nonpsychiatrists, and that what sympathetic and interested dermatologists and allergists were already doing in the way of routine care satisfied their needs to some extent.

Wise physicians are no doubt aware of this. Any dermatologist who has thought about it as he cares for a case of raging, flaming atopic eczema, sometimes with a feeling of "having a bear by the tail," knows that if he hangs on, the beast will wear itself out eventually. But in all honesty, it must be admitted that one still doesn't cure cases of atopic eczema. One carries them through episodes of the disease, sometimes short, sometimes long. This is done largely by the art of medicine, with the help of steroid hormones, antibiotics, skillful use of local medications, roentgen therapy, and occasionally by elimination diets and desensitization procedures.

In searching for a more definite and precise application of the art, group psychotherapy occurred to us. For a long time, the dermatologist in this study has been intrigued with the idea of getting these people together. It was hoped that they would gain some comfort by knowing that others suffer from this dreary, disabling disease. It is a surprising thing to discover, on questioning eczema patients, how

TABLE 1.—*General Data*

Sex	Age Range	Average Age	Single	Married
Female	15 to 49	28	7	18

Total No. Patients	Total No. Sessions (18 Mo. Period)	Average No. Patients Present	Largest No. Present at One Session
25	60	4	8

alone they feel in their misery. The psychiatrists saw it as an economical method of giving supportive psychotherapy to a large number of these people at one time, and at a level which was felt best suited for their needs.

CASE MATERIAL

This study has been carried out over a period of 18 months and during that time 25 atopic eczema patients began treatment. Because of our wish to provide a therapeutic setting most conducive to the open discussion of common problems, the patients were limited to the female sex.

At first, in an attempt to fill the group, cases of other obstinate dermatologic conditions such as pruritus pudendi, chronic dyshidrotic eczema and nummular eczema were included. However, it was soon decided that large numbers would serve our clinical research aim less well than would the opportunity to observe a smaller but more homogeneous group. Thus our statistics have been drawn from 25 atopic eczema patients.

Eighteen patients were married, 7 single; the youngest was 16, the oldest 46. It was found that the married and single women mixed together well, but two 16-year-old girls were rather out of place in an adult group. Interestingly enough, a woman and her married daughter attended for a period. There were two Negro women, only one being an atopic. The other, who had lichen chronicus simplex of both elbows, dropped out after six sessions—the lesions had disappeared. The participants were recruited mostly from private practice, and their economic status and educational backgrounds varied widely. All of the atopic eczema patients were long-standing sufferers from their eczema, and they had experienced a variety of accepted therapeutic measures by dermatologists and allergists. Several had been hospitalized one or more times, and two of them had had prolonged care in psychiatric institutions because of episodes of depression. They were all more or less severely exacerbated at the time of starting with the group— to the extent that they could not carry on usefully in their capacities as students, housewives, or in private employment.

METHOD

We had hoped that the group setting would be conducive to interreaction among the patients —the accepted mode in group therapy. We would have preferred to stay on the sidelines, only occasionally intervening in the situation to direct discussion or to mediate differences among the patients. The opportunity would thus be presented for the patients to discuss personal issues of either dermatological or psychiatric nature in the presence of physicians in those respective fields.

We were thwarted from the beginning in our attempt to be passive. The patients continually maneuvered one or the other of the therapists into a position of leadership. This brought about a change in the tactics. The dermatologist more actively assumed the role of the physician, offering help and encouragement, while the psychiatrist remained the less active.

The sessions began with the dermatologist inspecting each patient and commenting on her individual progress—any lack thereof was not voiced. This would usually give rise to the same questions and comments that dermatologists encounter in dealing with these patients, about the relative value of various local applications and dietary restrictions and the effects of weather and season on the skin. We would allow this to go on for a period, and, when the opportunity presented itself, discussion was led into more personal matters.

We acquainted each patient, when she began, with our convictions about the influence of her personal difficulties on the comings and goings of the eczema, yet the group repeatedly had to be led into discussions of such matters throughout the sessions. Sometimes participation was lively and spontaneous; at other times the group would be strikingly uncommunicative.

The sessions lasted an hour and were held once a week. A total of 60 were held and attendance varied widely. The greatest number present at any one session was eight, and occasionally only one or two attended. The meetings were held in a room in the University Dermatology Clinic, attended by two of the writers consistently—one or the other was only occasionally absent. The proceedings were recorded in longhand, and they constitute a running account of the activities. They were the basis of the following observations.

GENERAL OBSERVATIONS

Most of the atopic patients were fairly enthusiastic about the idea when it was first suggested to them, and they joined the group readily. A few expressed reluctance; one compared it with a drunkard's hesitance to enter Alcoholics Anonymous.

They were all diffident and reserved in their first few sessions. However, we noticed that they soon developed a tendency to foregather in the waiting rooms. The sessions were held following the dermatology clinic, and our group subjects would be dispersed among all the other patients while waiting. They showed a rather surprising tendency to seek each other out, and a number became quite friendly. They would come early and chat, dropping out for coffee before and after the meetings. In a few instances, the women kept in touch with each other outside of the clinic, visiting or communicating by telephone. This camaraderie was much less evident while they were in this group situation.

Generally, even casual conversation had to be initiated by us. In the earlier sessions, the nonatopics who were then present would do most of the talking, and they were easily guided into personal and emotionally charged subjects. They would readily discuss their home life, their family and other relationships; while the atopics listened in frozen and, what appeared to be, disdainful silence.

The atopics could and did chatter interminably about their pruritus and scratching, when invited. They would do so when questioned on entirely unrelated matters. They would describe their cutaneous symptoms with vehemence, but when asked about their life situations, their inner thoughts, and feelings, they seemed puzzled. They would not really answer such questions, but would lapse into detailed descrip-

tions of how they itched and scratched. This seemed not to be a conscious resistance to such probings; rather, they were truly unable to talk about themselves other than at a somatic level.

We began this project with the idea that through encouragement from us and from group interplay, these people would be able to discuss matters that we knew troubled them—their fears, their feelings about family members, their inability to express usefully anger or love, their moods of depression. We had hoped they would gain benefit from self-recognition in other patients. They did not all do this, by any means, but some did respond in a certain fashion, and with that response there was noted interesting progress in their eczema.

Table 2 attempts to correlate behavioral change, as observed in the group setting, with our estimate of skin improvement. From the starting point of a remarkably uniform group of people who were found to be peculiarly nonverbal, wooden-faced, and emotionally frozen, we noted that many of them began talking much more freely than we had thought possible; a lightening of mood became evident, and they seemed to gain in confidence. These were the patients who then showed progressive

TABLE 2.—*Group Situation Behavior in Relation to Eczema*

Behavior		Eczema		
		Improved	Not Improved	Not Evaluated
Increased verbal aggressiveness, Increased aggressive action, Decreased depression	8	8	..	..
Withdrew from group—open anger	3	3	..	..
Withdrew from group—concealed anger	4	..	4	..
No change in speech, behavior, or mood	2	..	2	..
Not evaluated (fewer than 5 visits)	6	..	..	6
Transferred to individual therapy	2	..	..	2
Total no. of patients	25	11	6	8

and often dramatic improvement in their eczema. During the course of the sessions, these patients grumbled openly, protested the lack of immediate symptomatic relief, were often sarcastic and openly belittled one or the other therapist, or instigated concerted attacks on us with the raising of such controversial questions as the role of food allergy in the etiology of atopic eczema.

Concurrently with the increase in verbal aggressiveness and associated physical animation, they were seen to pay more attention to their dress and grooming. We saw in this a marked contrast to the drab, defeated, and colorless attitudes of these same patients when first seen. Three of them, as the acute distress of the eczema subsided, made profuse use of puns and humor. They lampooned acquaintances, obnoxious family members, and other physicians with little reservation. But it is noteworthy that little direct hostility came out in relation to others in the group.

The common denominator of a frictional relationship with a parent or other key figure was frequently affirmed in vociferous detail by these improved patients. Often the bulk of an hour would be dominated by one or another pleading the cause of neglect or oppression.

Three patients, who rapidly became openly demanding and angry toward one or both therapists, refused to continue with the group despite objective evidence of skin improvement. Follow-up contact with them has found both the anger and the lessened degree of eczema to have continued. From this we gained considerable

insight into the prime difficulty in dealing with atopic eczema patients in general. Their helpless dependency and lack of responsiveness to treatment in the face of strenuous therapeutic efforts, along with persistent demands for relief, are most conducive to anger on the part of the physician, whether he is consciously aware of it or not. We believe that the essential iatrogenic aspect of treatment failure, in relation to these patients, involves the same sort of reciprocal hostility that is set up in their early life relationships. The end-result is some form of rejection and the ruination of therapy. These are unusually taxing people who wish for almost unqualified acceptance, with little or no demand placed upon them.

Four patients withdrew from treatment without having given open expression to their feelings about themselves, their skins, or the group. There was no change in the eczema.

Despite regular attendance for many months, two unexpressive patients remained unaffected by either group activities or medical efforts directed toward amelioration of skin symptoms. They showed no change in speech, behavior, or mood.

Six patients have attended less than five sessions at the time of this writing, and although each is following one of the several alternative patterns outlined above,

TABLE 3.—*Social Situation Behavior in Relation to Eczema*

Behavior		Eczema		
		Improved	Not Improved	Not Evaluated
Increased verbal aggressiveness Increased aggressive action Change in social relationships	11	11	..	..
No change in speech, behavior or relationships	6	..	6	..
Not evaluated (fewer than 5 visits)	6	..	..	6
Transferred to individual therapy	2	..	..	2
Total no. of patients	25	11	6	8

we are not sufficiently acquainted with them to more than prognosticate concerning the outcome. Two who were teen-aged and had little in common with the rest of the group were transferred for the purpose of individual, supportive therapy.

Table 3 demonstrates the fact that these patients carried similar reactions to those we observed in the group situation into their everyday living. Those who had become more aggressive in the group also began dealing more effectively with vexing environmental situations. "Now I tell people off—I'm not so self-conscious any more"; "She doesn't bother me now." These became familiar phrases in their conversation. Four of the 11 effected drastic changes in their social relationships by managing to sever a chronic, frictional relationship with their mothers. Two, who were single, moved to another community, sought jobs, made new friends and are planning marriage. The other two, who were married and had children, moved out of the parental home in an unprecedented show of independence. Each, now in open revolt, ended years of subservience to mother, and proceeded to establish healthier relationships with spouse and children.

The six patients who maintained their passive, inarticulate, and depressive adaptations in the group setting were those who had not come to the point of more effective dealing with unrewarding and unyielding life situations. They seemed caught in a static, dependent attitude and were somehow unable to profit by our intention to help them. To repeat, it was with them that our shortcomings became

apparent, and it seems that unwittingly we had played into interactions that were reminiscent to them of earlier unpleasantness. These patients showed little change in their degree of skin involvement.

As in Table 2 six patients were not evaluated because of inadequate information regarding them, and two patients were transferred to individual therapy.

Table 4 is intended, in a highly condensed way, to locate atopic eczema in a psychosomatic frame of reference. In this schematic stratification of human maturation, adapted from concepts set forth by Jurgen Ruesch,[12] normal development is seen as a progression from a nearly helpless immobility in which all needs must be

TABLE 4.—*Levels of Emotional Expression*

Level of Expression	Normal for	Characteristics	Typical Psychosomatic Responses
Organ Level (fight or flight)	Infancy	Discharge involuntary via autonomic nervous system: sucking, swallowing, regurgitating; constipation or diarrhea; heart rate or blood pressure changes; skin sweats or parches, flushes or blanches; endocrine changes; body fluid changes	VEGETATIVE DISORDERS: Peptic Ulcer Syndrome; Hypertension; Angina Pectoris; Allergy: Asthma, Urticaria, Vasomotor Rhinitis; Atopic Eczema
Action Level	Early Childhood	Discharge under cortical control via voluntary neuromuscular system: actions permit maximum tension discharge - at first egocentric and aimed at quick satisfaction. They may incite increased tension through conflict with reality.	ACTION DISORDERS: Alcoholism; Over-eating; Perversion; Aggressive Reactions; Criminality
Substitute Level	Later Childhood	Inhibition of action: tension discharged via speech, thought and phantasy; tensions may be repressed, suppressed, or converted into disguised substitutes when unacceptable to reality.	SUBSTITUTION DISORDERS: Compulsive Personality; Phallic Personality; Obsessive-Compulsive Reaction; Hysterical motor and sensory disturbances
Mature Level (Sublimation)	Adult	Action is appropriate: solves or alleviates tension within reality demands.	Anxiety Symptoms in reaction to situational stresses

This table depicts four major levels of personality development and compares successive levels of emotional expression in the left-hand column of cartoons with typical psychosomatic responses on the right. The helpless infant on the left is the archetype of the scratching eczema patient on the right who is overwhelmed by adult responsibility, an indifferent husband, and a dominant mother. The little girl who directly assaults her rival on the left has her parallel in the eczema patient who, in the beginning of skin remission, breaks into open revolt against her ungiving mother. The more socialized expression of aggression at the substitute level finds its corollary in the eczema patient, now in remission, who has reached an equilibrium as a compulsive housewife. Maturity is depicted as a relatively stable adaptation in a setting of personal achievement.

sensed and satisfied by the environment, through a phase of self-satisfying actions which slowly are "civilized" by environmental pressures, to the point where needs are quickly and efficiently met by the individual through his learned interactions with the environment.

A broad spectrum of human behavior can, with limitations, be spread out in reference to this progression. The fairly mature person, under external threat or inner pressure, may sample briefly the "organ level" responses as part of his initial

"fight or flight" reaction, but he has at his disposal such a varied and adaptable set of learned responses that he can quickly move from immobility to the appropriate action whereby his tensions are discharged and equilibrium with his environment restored. The classically neurotic person sacrifices this problem-solving action for less efficient substitutive behavior which gives mainly symbolic expression of the problem rather than a solution. The behavior problem "acts out" his tension discharges either openly or disguisedly against his environment. The psychosomatic sufferer exhibits a sorely limited repertoire of ways of expressing his needs; he is thus immobilized in a state of dammed-up tensions which contribute their share to the etiology of his disease.

The right-hand set of cartoons endeavors to depict the typical pattern of movement of the atopic patients of this series concurrent with their clinical improvement.

Regarding those cases with which we are familiar enough to discuss with conviction, the following findings are suggested. In an eczematous exacerbation, the patient exhibits many signs of having regressed to a state of helplessness that has its closest parallel in either actual infancy or other incapacitating disease states. The acute and severely ill eczema patient is generally immobilized both by the eczema and by his struggle to handle his strong feelings of rage and dependency. In his discomfort he is unable to act effectively to satisfy his wishes—others must serve him. In his incapacity he is dammed up and dissatisfied, and emotional expression finds discharge in a primitive way—through the organ of greatest physiological vulnerability. The complex factors that are thought to determine organ selection will not be discussed in this writing.

A number of our patients evolved a pattern of acting out their previously inhibited anger first by verbally battling the dominating attempts of others, then tearing dependency ties to parents or parent figures, and maneuvering into positions of greater social independence. Once the process was under way, they maintained gains by various defense mechanisms. Compulsive traits, for example, were used strenuously by some patients in a more covert binding of their aggressive strivings and were manifested by perfectionism in work, greater neatness, or scrupulous housekeeping. Sarcasm and joking helped to release hostility in a somewhat socially acceptable way and served to fortify previously concealed wishes to dominate.

Our patients who showed skin improvement were those who used aggressive techniques to solve their poblems, and we saw little emergence of other physical symptoms. Only two patients developed transient substitute symptoms when their improved adjustment was threatened. The one developed headaches in relation to the frustration of her wish to become pregnant, while the other complained briefly of a bizarre symptom complex that impressed us as being a conversion disorder. She was struggling to manage an independent household after having moved her family out of the parental home.

Thus we have seen the improved patients move from the adaptive level of a severe vegetative disturbance to marked skin improvement associated with aggressive and, for the most part, constructive action. We had previously observed in the life histories of many eczema patients that childhood, the period of most permitted aggressiveness, was attended by mild or no skin difficulty. Infantile eczema often abates in childhood to reappear at some point in adolescence or later in con-

junction with one aspect or another of the threat of separation from a dependent relationship. This observation is also borne out by knowledge of several patients who have been studied individually. They have histories of freedom from eczema in adulthood while involved in sprees of rebellious or delinquent behavior. None of the cases here reported have reacted so extremely as to become classified as having disorders such as alcoholism or criminal reactions.

Whatever the physiological, anatomical and immunological forces which predispose, it seems that fluctuations of this disease in adult life result from the patient's relative ability to maintain a state of equilibrium by the use of defense mechanisms that bind or satisfy persistent infantile wishes. The failure of defenses, in the face of the threat of disruption of often realistically unpleasant dependency ties, results in skin exacerbation, repressed anger, and the emergence of depression.

SUMMARY AND COMMENT

The ideal in presenting a therapeutic approach to any disease is to be able to talk statistically, to break down the cases treated into those cured, improved, and not improved. As of now, there is no pat method of managing atopic eczema. It is an episodic disease in which the patient is subject to recurrences, and those who have it in adult life experience one or several exacerbations. Rarely is the disease seen beyond the third or fourth decade of life.

In most of our patients, we have applied this method during one episode of the disease in their adult life; a few have participated in the group during a second or third episode. Thus, we are not in a position to make sweeping statements about what effect our method has had on the natural history of the disease—we are dealing with reversible reactions.

We feel that we can say this: initiated by the superficial observation that there was something unusual about the personalities of people subject to severe episodes of atopic eczema, an observation that was verified and specified by careful psychiatric appraisal of a number of them, group psychotherapy was tried in an attempt to help them improve their relations with people and situations. While these patients were in the group situation emphasizing strong emotional support and encouragement to ventilate, a definite change was observed in a large number of them. There was noted the emergence of aggressive speech and action, a lifting of depression, increased attention to make-up and dress, and return to vocational activities.

We have been encouraged by the unexpected number of improved patients in this study and equally concerned at our failure somehow to reach many others. We have found it difficult to form even a superficial relationship with these covertly hostile and demanding people who have been not only hurt in their earliest relationships but have become guarded, suspicious, and distrustful during their years of protracted treatment in quest of the magic of relief. In regard to our treatment failures, it has become evident that we did not give them something that was needed. It seems rather that some of the patients managed to evoke hostility in us and some manner of rejection. We have come to learn that the primary rule in dealing with them is unequivocal acceptance, without the demand of their immediate response. It must be remembered that communication is carried on at more than one level and these nonverbal people readily sense anger in others. In regard to

the patients who withdrew from treatment, it is clear in retrospect that a major tactical error was made in not replying directly to many of their implicitly hostile questions. The illusion of nondirective therapy and the turning back of questions were based on annoyance, denied though it was, on the part of the therapists.

In this study group, therapy came to mean a technique whereby the idea of comprehensive medicine could come to closer realization. Most of our patients were given routine dermatologic care during the group treatment. In fact, this service, at clinic fee levels, was an initial resort to interest many of them in the project. We profited by our beginning mistake of too little preparation for the group by arranging for psychiatric appraisal, psychological testing, and an interview with a social case worker. Through this process, we gained in understanding, and the patient was given sufficient opportunity to discuss her views of the treatment procedure. As our experience with the group accumulated, we were able to provide more acceptable support in terms of education, persuasion, and reassurance.

We feel that the group method is advantageous from the standpoint of both physician and patient. It is economical in terms of time; yet it can be aimed to give much to the patient from both the dermatological and psychiatric standpoint. The team aspect not only has provided better service to the patients, but has operated to share the medical responsibility and thus lessens the treatment hazard of hostility toward difficult patients. A sound working relationship between the dermatologist and psychiatrist is of fundamental importance in tailoring a satisfactory situation.

CONCLUSIONS

1. The comprehensive treatment of atopic eczema is best served by a therapeutic regime that includes both dermatological treatment and supportive psychotherapy.

2. Group psychotherapy, modified to meet the special needs of a relatively homogeneous test group of female atopic eczema patients, has proved to be an effective treatment method.

3. The establishment of a satisfactory working relationship between dermatologist and psychiatrist, in a common setting, has combined to give more adequate service than either discipline has provided when working in isolation.

4. Adequate appraisal of the patient is a requisite to selection of the most appropriate form of psychotherapy. Although group psychotherapy may provide optimal emotional support as well as maximum economy, individual psychotherapy remains more acceptable to certain patients.

5. Therapeutic success appears to bear heavily upon the physician's ability to cope with the excessive demands and the well-known unresponsiveness of these patients. An iatrogenic factor stems from unconscious hostility and some form of rejection of the patient by the physician.

6. Remissions of atopic eczema occur when frictional dependency ties are severed, compensatory emotional support is gained, and infantile wishes find greater satisfaction in aggressive outlets

ABSTRACT OF DISCUSSION

DR. DONALD H. WILLIAMS, Vancouver, B. C.: It is a pleasant task to be associated with Dr. Ray Noojin in introducing the discussion on Dr. Guy's first presentation before the Association.

The Greeks always had a word for it. Man, they described in total concept as being made of a soma, a psyche, and pneuma—a body, a mind and a soul. Dr. Guy and his associates have chosen to work on the relatively new hinterland between the soma and the psyche, on a particularly difficult part of the terrain with a technique new to dermatology. Dr. Guy's paper is in the nature of a preliminary report of a pilot effort, based upon earlier published basic studies on the personality of the atopic individual. The enlarging investigative effort is proceeding and until this is recorded, it will be difficult to assess fully the significance of this unique venture into group psychotherapy in atopic eczema.

Dr. Guy and his associates indicate that they are fully aware of the pitfalls of research in the psychosomatic field. They clearly see the problem of controls and variables. They recognize the difficulty of applying the scientific method and discipline. A sigh can't be weighed in a balance nor the intensity of anxiety determined in a colorimeter. The nature of atopic eczema and the inherent compulsive temperament of patients suffering from it make group effort with these persons a trying experience. In the face of these obstacles, the investigators are to be highly commended for the early valuable results of the study which in no small degree stems from their own qualities of sincerity, tenacity and, above all, the large measure of warm understanding and the milk of human kindness so evident in their report. These attributes assure success of the extension of the group effort in further worrying the barbed porcupine of atopic eczema.

A fascinating feature of this dermatosis is the rhythmic seasonal groundswell of atopy upon which the clinical turbulence appears. I have noted in hospital wards that as the leaves begin to flutter earthwards in the fall, the atopics begin to fill the beds and as soon as April brings the honking of northward-moving geese, the atopics, like Arabs, albeit itchingly, fold up their tents in the night and silently disappear. I should like to ask Dr. Guy whether this seasonal factor played any role in the improvement of his patients? Did the articulateness, the aggressiveness, and the lifting of depression which appeared with clinical improvement of the atopic eczema coincide with the end of winter?

Dr. Guy and his associates have stormed with great courage a heretofore impregnable bastion. Dr. Guy has presented a paper that is in the best tradition of American dermatology, as befits the son of an illustrious father.

Dr. Ray O. Noojin, Birmingham, Ala.: The authors have emphasized the psychoneurogenous mechanisms that are commonly found operative in the patient with atopic dermatitis. In consideration of their therapeutic approach to this problem, the question arises again as to the etiologic mechanism or mechanisms that must be active in the cause of this dermatosis. The consensus has maintained that there are three major characteristic components of the disease, namely, specia! responses of the skin to different stimuli, systemic allergic responses, and neurogenic features. The hyperreactivity of these patients usually is extensive, and this characteristic tendency to react is ordinarily of greater importance than the items to which they react.

The title of this paper is in itself thought provoking. The question of terminology has actually never been definitely settled as to whether this dermatosis should be called atopic dermatitis or disseminated neurodermatitis. Some investigators strongly believe that psychiatric studies have not only failed to clarify these dermatologic cases as regards etiologic mechanisms, but that the psychiatric approach has likewise consistently failed therapeutically. On the other hand, it seems only fair to emphasize the fact that dependence upon determining the nature of causative allergens and subsequently eliminating them from the patient's existence has likewise often proved disappointing from the standpoint of therapy.

It appears that the only logical answer to be given to this problem at the present time is to consider the psychoneurogenous and the allergic factors merely as component parts of this complex of agencies and to include also the bacteriologic, immunologic, hereditary, and pathogenic factors.

The results obtained by the authors in their use of group psychotherapy warrants careful consideration. For the psychiatrist this is not a new approach. In psychiatric studies of other problems the benefit of "universalization" has been emphasized. It has been thought this therapeutic mechanism makes the group more cohesive. Patients seem to be aided through the identification of their own problems as seen in other members of the group. After the patient perceives his own problem in another person it tends to lead to a reduction in tension. It leads to a feeling of social equality with others, and this may be quite different from that experienced by the patient in his own customary environment.

Since group therapy, therefore, has been effective in the management of other medical problems, its further investigation in dermatology appears to be of value.

Several suggestions might be considered in continuing a study of this type. It seems important that the groups be limited to patients with atopic eczema only in order that all patients would have this same factor in common. The groups should be sufficiently small so that the individuals will have a closer association with each other for the purpose of effecting a change of attitude. It might be well to remove the sessions from the dermatology clinic to a meeting place removed from medical atmosphere. This would also increase the social aspect of the sessions. Another group, for the sake of comparison, should be investigated in which the sexes were mixed. This might even further stimulate the patient to look his best. It seems worth while to make strong attempts to move leadership in the sessions to the patients themselves and away from the therapist. The authors are to be commended for the work they have done thus far, and it seems worth while that these limited studies should be continued.

DR. MAXIMILIAN E. OBERMAYER: Not much is gained by saying that "atopic eczema is truly a psychosomatic disease." Such statements may be misunderstood and antagonize the worker whose efforts have been directed toward uncovering the many organic factors in this disorder. The emotional and psychic structure of the patient with neurodermatitis is merely one aspect of the syndrome, although the piling up of neurotic tensions is undoubtedly a primary factor in precipitating exacerbations.

During a three-year investigation of the personality structure of patients with neurodermatitis by means of psychiatric interviews and projective tests, my own research group determined that certain emotional peculiarities distinguished them from persons without neurodermatitis. On the basis of these differentiating features, we attempted to formulate theories as to psychosomatic interrelations in patients with this disorder. Group therapy was a most useful tool in this project; by such means, we were able to chart emotional fluctuations and to evaluate such records statistically.

Dr. Guy and his colleagues have stated that patients with neurodermatitis are unsuited to deep level therapy. This view has been expressed by Macalpine repeatedly. She has postulated substantial psychoanalytic reasons for the therapeutic failures, but the validity of her reasoning is questioned by some psychoanalysts. Be that as it may, the failure of deep therapy would seem to imply that even though the therapist may fully appreciate the psychic mechanisms by which the patient produces his symptoms, the patient himself seems unable to benefit and to change. Perhaps the concepts and technics of therapy have not been adequately adapted to the patient with neurodermatitis. This is one of the problems on which—we hope—our study may throw light.

Dr. Guy and his collaborators found group therapy of value in providing desirable emotional support—an observation that agrees with the findings of my co-workers and me. In group therapy, the patients find mutual support, sympathy, and identification. As a result of the development of this mutual interest, other emotional expressions are exchanged and revealed; meanwhile the therapist clarifies and interprets these expressions and reassures the patients. In the group studied by us, improvement in the dermatosis was recorded on the release of certain specific emotions but before any insight occurred. These specific emotions we shall try to define in our forthcoming publication.

I have enjoyed hearing this paper, and hope that Dr. Guy and his co-workers will continue their constructive efforts.

DR. FRANK E. CORMIA, New York: I should like to congratulate Dr. Guy for giving us this new approach to the management of the atopic type individual. I think it is quite a significant contribution.

It is of significance, too, that his successes were only partial, and I think the reason is that in atopic dermatitis, there is no specific personality type. Dr. Obermayer commented on this point a few years ago and I have found the same thing. It is true that the clinic type of patient is rather depressed and lacking aggression, but the average patient seen in private practice is quite different. They are more aggressive, and they, perhaps, hurt themselves by their aggression. Therefore, there may be some limitation to a procedure which is directed primarily at depressed individuals.

I have found too, that individual psychotherapy may not be successful in this group of individuals. However, some patients who have had adverse life situations for long periods of time may do extremely well if they are given prolonged hospitalization in a psychiatric institution.

Dr. Noojin has pointed out very adequately that atopic dermatitis is not a single-faceted disease, and I think that we must agree with this concept. Who could have heard Dr. Osborne's paper last year without feeling quite strongly that there are allergic factors which are operating in this disease? So many times, we see patients who are treated by allergists; frequently, we find they are sensitive, let us say to wool. When they are given an injection of wool allergen, a severe flare-up may ensue. How can this be explained except on the basis of specific sensitivity to that particular substance?

In addition, it is well known that a temporary change in environment to Texas, Florida, or Arizona results frequently in marked improvement. The allergist will say that the patient has been separated from his allergens, while the psychiatrist will insist that he has left his troubles at home. But there is another factor, pointed out, I think, by Dr. Sulzberger and others. These patients with severe atopic dermatitis have considerable sweat retention. If they move to a cool, dry environment, this factor frequently can be controlled.

One can discern, in this disease, therefore, multiple etiologic factors operating together in a most complex fashion.

Dr. Joseph V. Klauder, Philadelphia: I am sure we all appreciate and are indebted to Dr. Guy for his penetrating study of the psychogenesis of atopic dermatitis; I hope he will continue a similar study of other dermatoses.

I think it is desirable, in discussing psychotherapy, to define the term: what one means by psychotherapy. Is a "pep" talk to the patient psychotherapy? Is assuring the patient he is going to get well psychotherapy? Is a pat on the back or direct or indirect suggestion psychotherapy? That is not the sense that Dr. Guy is using the term, and it is not in the psychiatric sense. The psychiatric sense, as I understand it, is an endeavor to impart to the patient the psychogenesis of the mechanism as an explanation of his symptoms, to enable him to get an insight into and to appreciate such psychiatric terms as "sublimation," "projection," and "rationalization" and terms of that nature.

I have been interested in group psychotherapy ever since I attended my first meeting of Alcoholics Anonymous—not as a member but as a spectator. These meetings are admirable examples of psychotherapy, and I suggest that you attend one or more. They take place in most large cities. No ticket of admission is necessary; you just walk in. It is interesting to hear the narration of the experiences of an alcoholic—what motivated him to get drunk and the means by which he is alleged to be cured. That is real group psychotherapy.

After attending those meetings, I thought, "Why could not these principles be applied to certain dermatologic patients?" so I started group psychotherapy among private patients, in a very small way, in an amateur way, and I suppose the psychiatrists would call it just a "pep" talk, but my concept was this: To have a group leader, an intelligent person, who has considerably improved or recovered from a certain type of dermatosis. One group leader was a young woman with atopic dermatitis whom I treated over a period of years. It disappeared when she entered a convent. One would think that the solace of a religious life was helpful, but apparently that was not so because she left the convent and got married, and the atopic dermatitis never came back. She was an excellent group leader.

The meeting place is your office, outside of office hours, and to make it a social affair, divorced from medical aspects, tea is served. Your nurse and secretary are present. You select three or four patients to attend the meeting. My concept is to select patients on the same cultural or social level. The group leader does much of the talking, which you direct. You know in advance what the leader will say since you coach him in advance. In that sense you stack the cards against the other patients. But after all, is not psychotherapy stacking the cards?

My other group leader—and this is most complimentary to our able colleagues at the Mayo Clinic—is a young man, a former patient of mine, who subsequently was a patient at Mayo Clinic and returned to me as a patient. He was remarkably changed. He had an entirely different mental poise and had a tremendous insight of the psychosomatic aspects of atopic dermatitis. He rehearsed to me the psychotherapy he received at the Mayo Clinic, and for that reason I think Dr. Brunsting should discuss this paper. This young man is an excellent group leader.

I think group therapy can be extended to other diseases of the skin. For example, I thought of utilizing it for patients with circumscribed neurodermatitis. I hope Dr. Guy will consider this and extend his study to other diseases of the skin. For those interested, I would suggest a book (Hinckley, R. G., and Herman, L.: "Group Treatment in Psychotherapy," Minneapolis, University of Minnesota Press, 1954).

DR. JACOB H. SWARTZ, Boston: I, too, enjoyed Dr. Guy's paper. I have been interested in his work for a long time, especially the animal work.

I would like to suggest just one more mode of psychotherapy. In the cases I have followed, I find that a daily diary is a very useful method in handling these cases. At the beginning, these patients will not open up, perhaps, but after a while it is surprising how much they will pour out and how helpful it has been after several months. You have to gain their confidence. They won't come to you if you don't. The daily diary has proved very useful as a ventilating therapy.

I also think that the parents of the patient sometimes need psychotherapy more than the patient. The daily diary helps to determine this.

Dr. Williams mentioned seasonal variation. I think the psychiatric factor can also explain this in part. Most people do relax more; they throw off their responsibilities, in the summer, naturally, regardless of how much they have. Maybe that is a factor in affecting an improvement in the summer in some cases.

I recall that my former teacher, Dr. Charles J. White, used to examine the stools of infants with eczema, and even of the older children, for fat indigestion, carbohydrate indigestion, etc. In my experience, a change of bacterial flora in the lower bowel helps. These bacteria need not necessarily be pathogenic bacteria. Bacterial allergy, has, in my series of cases, proved an important factor in some of these cases. I studied the intestinal flora, trying to change it either by diet or by other methods, and, together with the psychotherapy, it has proved of some value in some cases and of great value in other cases.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: There are two fields of medicine which, of all others, are least likely to lend themselves to proper scientific control. One is allergy, the other is in the field of psychoanalysis. Statements can be made which can hardly be refuted. It is a truism to say that when one begins to be interested in a field, the favorable therapeutic results immediately jump 50%. We should, therefore, be cautious in drawing conclusions from the results of treatment in patients who have atopic dermatitis.

These patients are peculiar persons, indeed. They have disturbances of behavior but they also have measurable abnormalities such as the presence of certain reagins, abnormal physiologic responses, and, occasionally, the formation of cataracts.

One of the outstanding characteristics of atopic persons is their attitude of dependency. The psychiatrist makes use of the device of transference of dependency by various means. The average dermatologist is not equipped in time or attitude to assume the responsibility for this management.

The trouble is not in the skin alone. Proper care of the skin and a healthy mental outlook are two of the requisites which will enable these patients to live within their limitations and enjoy a reasonable existence.

DR. WILLIAM B. GUY, Pittsburgh: I certainly appreciate and am further stimulated by the remarks of the above discussants.

Like the Greeks, Dr. Williams, too, is ready with an apt word. The figure of the "prickly porcupine" that he applies to these people is as good as his figure of the "wondrous elephant" applied to the disease itself in a previous paper.

In answer to his question about the seasonal fluctuations of this disease, our group dwindled down to two, one, or occasionally no patients during the spring and summer months. In October and November they would return. This is certainly mysterious, and the recent work of Dr. Osborne on the effect of wool fibers in the air on this disease perhaps sheds some light on the fact.

The thought has struck me, with my psychologic orientation, that warm weather is generally a happier time for everyone; that with sunny days and outdoor activities, one's spirits are lighter. Certainly exacerbations of atopic eczema are associated with moods of depression. We haven't yet been able to decide even after this much study of these people, which comes first, or as remission appears, whether the eczema or the depression lightens first.

As to the question raised by Dr. Noojin about terminology—the psychiatrists I have worked with are much confused by our nomenclature. They want to know what we mean when we interchangeably use atopic eczema and disseminated neurodermatitis. When we throw in circumscribed neurodermite and lichen chronicus simplex, it about overwhelms them. Nondermatologists in general join in this bewilderment, I'm sure.

Originally I shared Dr. Noojin's view that he made in one of his suggestions. I wanted to socialize these sessions and have somewhat of a tea-party atmosphere. The psychiatrists inveighed against this and particularly were opposed to mixing the sexes. It seems that mixed groups develop romantic complications, and this is a distracting factor. Furthermore, Dr. S. William Becker, in a personal communication about our work pointed out another objection to this. He mentioned a novel published some years ago titled "September Remember" which dealt with the tragic marriage of two members of Alcoholics Anonymous. To produce a situation which might result in matrimony between such fragile personalities as the people we worked with could be equally as tragic. The offspring which might ensue suggests the possibilities of a dermatologic nightmare.

Dr. Cormia talked about helping them gain insight into their difficulties. That we have not been able to do. In fact we don't believe they are capable of that for the most part. We tried repeatedly to get our prize patients, the ones who showed the most salutary improvement, to tell us in their own words what happened. They had only the vaguest ideas about it. We had to be satified with the fact that they were better, and form our own conclusions about the reasons.

I believe Dr. Cormia also remarked that in his experience clinic patients are similarly passive people, but that private patients are more aggressive. Our patients in this and previous studies have largely been recruited from private practice. Lack of aggressiveness is probably part of the explanation of clinic patients' economic status, which would hold true among atopic eczema patients as well as others.

Our severely exacerbated patients were verbally aggressive to the point of bitter complaints of how they itched and scratched. If they become aggressive to the point of belittling their physician or becoming openly critical, this is a healthy development we believe, and the physician should look on it as such.

In answer to Dr. Klauder's rhetorical questions, as to what constitutes psychotherapy and are dermatologists already performing that function, I hope that question is answered in the body of the paper. A pat on the back and an understanding smile are good medicine in any illness as he well knows.

Members of Alcoholics Anonymous apparently enjoy foregathering and listening to each other's histories. After sufficient experience, our patients seemed to want to get together, but they initially didn't seem to have much interest in each other's skin or situational troubles. I had hoped that when brought together these people would show mutual interest in each other and would be comforted to know that someone else suffered from this dreary disabling skin disease. Not at all. They disdained each other like circus freaks.

Dr. Swartz's suggestion about these patients keeping a daily diary is recognized by psychiatrists as good psychotherapy. They call it ventilation, and consider it a valuable technique for relief of tensions.

What Dr. Brunsting said in a few sentences is the very essence of our whole argument. If you are to discharge your responsibilities as a physician with these patients you have to be willing to assume a big burden.

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POSSIBLE DISCOID LUPUS ERYTHEMATOSUS IN NEWBORN INFANT

Report of a Case with Subsequent Development of Acute Systemic Lupus Erythematosus in Mother

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THE CASES herein reported are those of an infant born with an eruption on the scalp and face, which clinically and histologically was consistent with chronic discoid lupus erythematosus, and of his mother, who developed acute disseminate lupus erythematosus 11 months later.

REPORT OF CASES

CASE 1.—J. V., a 6-week-old white boy, was first seen on Nov. 3, 1951. The referring physician stated that an eruption was present at delivery but had become more livid, and the number of lesions had increased in the six weeks since birth. Gestation period had been full term and normal. Birth weight was 4 lb. 13 oz. (2,183 gm.), length, 18 in. (46 cm.). Physical examination was negative except for the skin of the scalp and face, which showed discrete, erythematous macules varying from 0.5 to 3.0 cm. in diameter. Scaling, follicular plugging, and atrophy were definite (Fig. 1).

Histologic examination of a scalp lesion showed relative and absolute hyperkeratosis, keratotic plugging, alternate areas of atrophy and acanthosis, and liquefaction degeneration of the basal layer (Fig. 2). The infiltrate was made up chiefly of lymphocytes and was largely perivascular. There was no evidence of collagen degeneration. The serum L.E. test was negative.

No treatment was prescribed except application of a bland ointment. At the age of 3 months, the lesions showed definite signs of regression and no new ones had appeared. By the fifth month of life, disappearance was complete except for slight atrophy of the skin at the sites of previous lesions. There have been no signs of recurrence.

CASE 2.—Mrs. A. V., aged 38 years, was apparently in good health until November, 1952 (11 months after delivery of the infant, Case 1), when she consulted her physician for symptoms of weakness, fatigue, and vague transitory pains in the joints. Leucopenia was the only abnormal finding at that time. There was no history of drug ingestion.

She was admitted to the hospital on June 25, 1953, by an internist. Ten days prior to admission she began having a moderate fever (100 F.). She felt "anxious and ill" and a "dusky flush" was noted on her cheeks.

Physical examination was essentially normal except for a few moist rales in the bases of the lungs posteriorly, painless, mild splenomegaly, and mild cervicitis.

Laboratory findings were as follows: a blood count of 4,250,000 RBC, 12.5 gm. (80.6%) hemoglobin, 2,600 W B C, with a differential count of polymorphonuclears 69%, lymphocytes 31%, stab cells 12%, and segmented cells 5.7%. Hematocrit reading was 28%, and the sedimentation rate (Wintrope corrected) was 22 mm. per hour. Serologic test for syphilis was

Drs. H. E. Cromer, G. W. Cleveland, and C. F. Pelphrey contributed technical data for this paper.

negative. Nonprotein nitrogen was 38 mg. per 100 cc., and blood cultures were negative. Agglutination tests for typhoid, paratyphoid, Proteus OX19, and Brucella abortus were negative. A smear of the peripheral blood showed a large number of specific L. E. cells (Fig. 3).

Urinalysis showed a heavy trace of albumin, 3 to 5 white blood cells and a rare red blood cell per high power field. A chest x-ray examination showed minimal cardiac enlargement, and, bilateral minimal pleural reaction and effusion. An electrocardiogram was normal.

Repeated blood cell counts showed no change from that noted above. The temperature on admission was 103.6 F., where it remained, except for spikes to 104.6 F., until response to therapy.

Therapy included routine supportive measures and cortisone. Initial response to 100 mg. per day was poor but was "dramatic" to 300 mg. per day. She was discharged after one month's hospitalization, symptom-free on a maintenance dose of 75 mg. of cortisone per day.

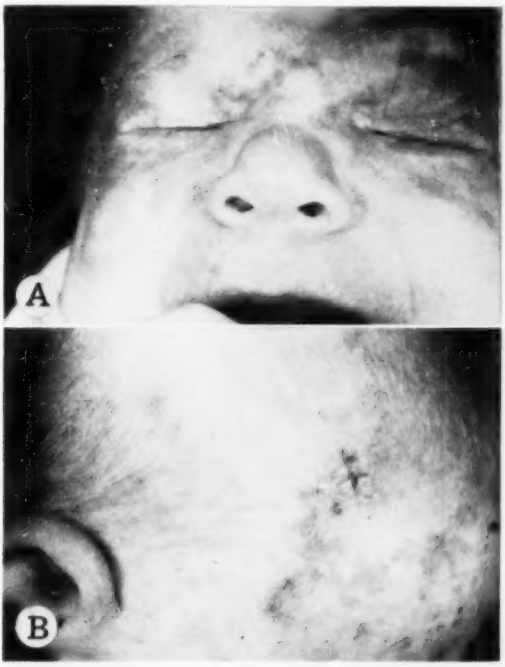

Fig. 1 (Case 1).—*A*, 6-month-old infant showing macular patches which were scaly, atrophic, and with gross follicular plugging. *B*, same patient; central area is healing biopsy wound.

COMMENT

The occurrence of lupus erythematosus in more than one member of the same family is relatively rare. Von Gruenhagen [1] reviewed 30 such case reports up to 1952, and reported cases of discoid lupus erythematosus in identical twins. Shearn and Pirofsky [2] reported the occurrence of disseminated lupus erythematosus in two members of the same family and reviewed three other similar reports. There are probably considerably more unreported instances; however, a search of the literature failed to reveal a similar sequence of events as noted in these cases of an infant and his mother. In the light of recent work by Moolten,[3] these cases would tend to lend credence to the possible presence of a transmissible etiological agent in lupus

Fig. 2 (Case 1).—*A*, histologic features showing hyperkeratosis, follicular plugging, alternate areas of atrophy and acanthosis, and banal infiltrate. Hematoxylin and eosin stain; × 100. *B*, same area, showing plugging and liquefaction degeneration; ×430.

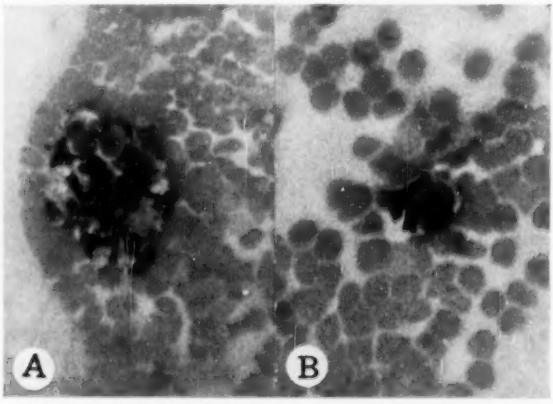

Fig. 3 (Case 2).—*A*, peripheral blood smear from 38-year-old mother showing rosette formation with formation of L.E. cells; Wright's stain, × 1,290. *B*, same smear showing single L.E. cell; × 1,500.

erythematosus. Was such an agent present in the mother's system 11 to 13 months prior to any clinical evidence of her disease? If it were present, did it pass the placental barrier? It has been shown that the L. E. factor may pass this barrier.[4]

There are numerous reports in the literature regarding the effect of lupus erythematosus on pregnancy. In those reports in which time of onset of the disease was noted, it would seem that the fetus is less likely to be affected when the lupus erythematosus appeared in the last trimester of pregnancy. However, when the disease appeared early in pregnancy, the incidence of miscarriage or still births seems higher. Unfortunately, we found no mention as to the presence of stigmata of lupus erythematosus in any of the stillbirths or products of spontaneous abortion. Ellis and Bereston[5] suggested that acute lupus erythematosus and even subacute lupus erythematosus might have a serious effect on the fetus, but they did not indicate whether the fetus in either of their two cases bore any stigmata of lupus erythematosus.

The histologic features of the biopsy specimen obtained when the infant was 6 weeks old answer the criteria of lupus erythematosus. Dr. Hamilton Montgomery reviewed the section and confirmed the histologic diagnosis. It is hazardous in this disease, as in many other disease processes, to be dogmatic as to correlation of the clinical phase and the histologic picture. We are unable to specifically type the disease stage in this infant.

SUMMARY AND CONCLUSIONS

Cases of a newborn infant with an eruption clinically and histologically consistent with lupus erythematosus and of his mother developing acute disseminate lupus erythematosus 11 months after delivery are presented.

It is urged that in the future in cases of death of a fetus of a mother who has lupus erythematosus of any type or who gives a history of this disease, the fetus be examined for stigmata of lupus erythematosus.

The possibility of a transmittible etiological agent of lupus erythematosus from mother to fetus is suggested.

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3. Moolten, S., and Clark, E., cited by Michelson, H. E.: Transmission of Lupus Erythematosus, Proc. Inst. Med. Chicago **19**:335-350 (Oct.) 1953.

4. Bridge, R. G., and Foley, F. E.: Placental Transmission of the Lupus Erythematosus Factor, Am. J. M. Sc. **227**:1-8 (Jan.) 1954.

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FURTHER STUDIES ON ANTIFUNGAL ACTIVITY OF SOME CINNAMIC ACID DERIVATIVES AND NITROSTYRENES

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THE SIMILARITY of the chemical formulae of the two stilbenes, (4,4'-stilbenedicarboxamidine) and diethylstilbesterol (4,4'dihydroxy-α,α'-diethylstilbene) was pointed out in previous papers * and their in vitro and in vivo activity against various pathogenic fungi was demonstrated. Stilbamidine has been used clinically in the treatment of North American blastomycosis with favorable results, but at the same time it has exhibited certain objectionable toxic properties, especially trigeminal neuropathy, and, with the present methods of administration and dosage schedules, post-therapeutic recurrences are not too uncommon.[8] The in vitro antifungal activity of diethylstilbestrol is greater than that of stilbamidine, but its clinical trials in the mycoses are not as extensive as those of stilbamidine. A definite deterrent to its use is its well-known potency as a hormone. These shortcomings led to further studies of the antifungal activity of other members of the stilbene group as well as related compounds, in the hope of finding substances that are more effective antifungal agents, less toxic, and without endocrine side-effects.

IN VITRO STUDIES

Materials and Methods.—Compounds with chemical formulae related to the stilbene nucleus were obtained from The Upjohn Company, Wm. S. Merrell Company, and the Dow Chemical Company. The procedure utilized to demonstrate antifungal activity was the serial dilution Sabouraud's agar method previously described,[2] in which the least concentration of the compound producing complete inhibition was considered the end-point. The compounds were first screened with use of five fairly representative species of pathogenic fungi—(1) Trichophyton rubrum, (2) Microsporum audouini, (3) Candida albicans, (4) Cryptococcus neoformans, and (5) Blastomyces dermatitidis—as test organisms. Compounds exhibiting promising results were tested against the rest of the pathogenic fungi.

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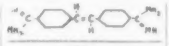
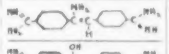
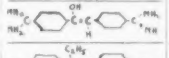
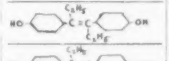
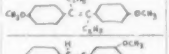
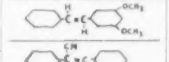
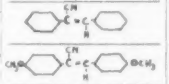
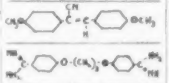
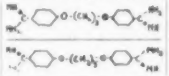
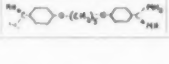
* References 1 and 2.

Results and Comment.—The results of the preliminary screening for antifungal activity of the available compounds are shown in Tables 1 to 4, which also include their individual chemical formulae to depict their structural relationships. The majority of the compounds were aromatic ethylenes. The stilbenes, aromatic diamidines, and cinnamic acid derivatives revealed varied amounts of antifungal activity, but the most striking activity was exhibited by the group of compounds belonging to the β-nitrostyrenes (Table 3).

Although the antibacterial activity of cinnamic acid, and its derivatives has been investigated by a number of authors,† relatively little work has been done on their action against fungi. Bonnevie [9] in 1936 compared the in vitro fungicidal power of

TABLE 1.—*Screening for Antifungal Activity of Certain Stilbenes and Aromatic Diamidines: Lowest Effective Concentration in Mg./Ml. Medium*

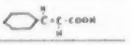
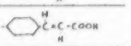
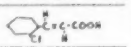
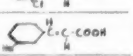
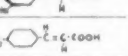
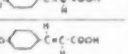
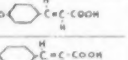
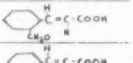
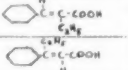
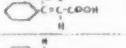
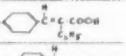
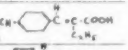
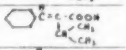
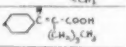
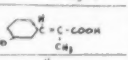
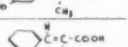
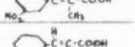
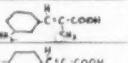
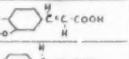
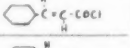
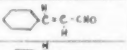
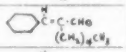
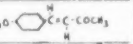
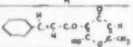
Compounds	Chemical Formulae	T. Rubrum	M. Audouini	C. Albicans	C. Neoformans	B. Dermatitidis
Stilbamidine (used as the isethionate)..		1.0	1.0	1.0	1.0	0.01
Aminostilbamidine (used as the hydrochloride)		>1.0	>1.0	>1.0	>1.0	0.1
Hydroxystilbamidine (used as the isethionate)		0.1	0.1	>1.0	>1.0	0.1
Diethystilbestrol		0.1	0.1	1.0	>1.0	0.01
Diethylstilbestroldimethyl ether.....		1.0	>1.0	>1.0	>1.0	1.0
3,5-Dimethoxystilbene		>1.0	>1.0	>1.0	>1.0	>1.0
Cyanostilbene		>1.0	>1.0	>1.0	>1.0	>1.0
4,4'-Dimethoxy-α-cyanostilbene		>1.0	>1.0	>1.0	>1.0	>1.0
Propamidine (used as the isethionate)..		1.0	1.0	>1.0	1.0	0.01
Pentamidine (used as the isethionate)..		1.0	1.0	>1.0	1.0	1.0

cinnamic acid with that of benzoic acid, salicylic acid, thymol, and ethylparabenzoate against the growth of Epidermophyton interdigitale (Kaufman-Wolf) and a yeast. He advised its use in dermatophytosis in the event of a sensitivity to salicylic acid. McGowan, Brian, and Hemming [10] evaluated a large number of organic compounds for fungistatic activity and found that a majority of the most promising compounds contained an ethylenic double bond. Included among these were cinnamic acid and certain of its derivatives. These authors used as test organisms three nonpathogenic species—Botrytis allii, Fusarium graminearum, and Penicillium notatum.

The antifungal activity of stilbamidine, propamidine, pentamidine, and diethylstilbesterol was discussed in a previous paper.[2] The additional data on 2-hydroxystilbamidine isethionate and aminostilbamidine hydrochloride (Table 5) point to a degree of antifungal activity comparable to stilbamidine isethionate. Snapper, Schneid, McVay, and Lieben [11] similarly found 2-hydroxystilbamidine to be as effective as stilbamidine in vitro and in a patient with South American leishmaniasis and

† References 4 to 8.

TABLE 2.—*Screening for Antifungal Activity of Certain Cinnamic Acid Derivatives: Lowest Effective Concentration in Mg./Ml. Medium*

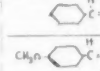
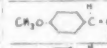
Compounds	Chemical Formulae	T. Rubrum	M. Audouini	C. Albicans	C. Neoformans	B. Dermatitidis
Cinnamic acid		0.1	0.1	1.0	1.0	0.01
p-Chlorocinnamic acid		0.1	0.01	>1.0	>1.0	0.01
o-Chlorocinnamic acid		0.1	0.1	>1.0	>1.0	0.01
m-Hydroxycinnamic acid		1.0	1.0	>1.0	>1.0	1.0
p-Nitrocinnamic acid		0.1	0.1	>1.0	>1.0	0.1
p-Methoxycinnamic acid		0.1	0.1	>1.0	1.0	0.01
o-Methoxycinnamic acid		0.1	0.1	>1.0	>1.0	0.1
α-Ethylcinnamic acid		0.1	0.1	0.1	1.0	0.01
β-Ethylcinnamic acid		0.1	0.1	0.1	1.0	0.01
α-Ethyl-*p*-chlorocinnamic acid		0.01	0.01	>1.0	>1.0	0.01
α-Ethyl-*p*-isopropylcinnamic acid		>1.0	>1.0	>1.0	>1.0	>0.001
α-Isopropylcinnamic acid		0.1	0.1	1.0	>1.0	0.1
α-*n*-Butylcinnamic acid		0.01	0.01	>1.0	>1.0	0.01
α-Methyl-*m*-hydroxycinnamic acid		1.0	1.0	>1.0	>1.0	0.1
α-Methyl-*m*-nitrocinnamic acid		0.1	0.1	>1.0	>1.0	0.1
α-Methyl-*m*-aminocinnamic acid		1.0	1.0	>1.0	>1.0	1.0
3,4-Methylenedioxycinnamic acid		0.1	0.1	>1.0	>1.0	0.1
Cinnamyl chloride		1.0	1.0	1.0	1.0	1.0
Cinnamaldehyde		>1.0	1.0	>1.0	>1.0	1.0
α-*n*-Amylcinnamaldehyde		1.0	1.0	>1.0	>1.0	1.0
Anisalacetone		0.1	0.1	1.0	1.0	0.1
2-Methyl-4-hydroxy-5-cinnamoyl-γ-pyrone		0.01	0.01	>1.0	>1.0	0.01
2-Methyl-4-hydroxy-5-(*p*-methoxy cinnamoyl)-γ-pyrone		>1.0	>1.0	>1.0	>1.0	>1.0
2-Methyl-4-hydroxy-5-(cinnamalacetyl)-γ-pyrone		>1.0	>1.0	>1.0	>1.0	>1.0

two with North American blastomycosis. They recommended the use of this hydroxy derivative of stilbamidine because it is more stable and less toxic.

The more complete antifungal spectra of monomeric styrene, β-bromostyrene and various β-nitrostyrenes are given in Table 6. The in vitro effects of the nitrostyrenes, except for *o*-methoxy-β-methyl-β-nitrostyrene, have been previously reported.[12] These studies suggest the antifungal activity is a group property of the nitrostyrenes against pathogenic fungi, except C. albicans, which, together with the saprophytic species examined, showed greater resistance to the action of antifungal agents. This resistance of C. albicans was noted in a previous paper [2] and by Christison and Conant.[13]

In a patent communication, Bousquet, Kirby, and Searle [14] report that they effectively used β-nitrostyrene and other compounds containing the nitroethylene radical

TABLE 3.—*Screening for Antifungal Activity of Certain Styrenes: Lowest Effective Concentration in Mg./per Ml. Medium*

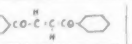
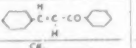
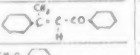
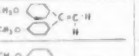
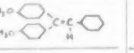
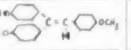
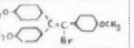
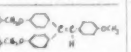
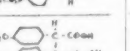
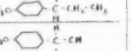
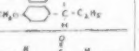
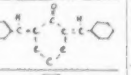
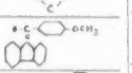
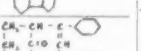
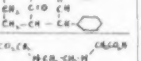
Compounds	Chemical Formulae	T. Rubrum	M. Audouini	C. Albicans	C. Neoformans	B. Dermatitidis
Monomeric styrene		>1.0	>1.0	>1.0	>1.0	>1.0
β-Bromostyrene		>1.0	>1.0	>1.0	>1.0	>1.0
β-Nitrostyrene		0.01	0.001	0.1	0.01	0.001
p-Methoxy-β-nitrostyrene		0.01	0.01	0.1	0.01	0.01
p-Acetoxy-β-nitrostyrene		0.01	0.01	1.0	0.1	0.01
β-Methyl-β-nitrostyrene		0.001	0.001	0.1	0.001	0.001
p-Methoxy-β-methyl-β-nitrostyrene		0.001	0.001	0.1	0.01	0.001
o-Methoxy-β-methyl-β-nitrostyrene		0.01	0.01	0.1	0.1	0.001

(—C=C—NO_2) as fungicides and pesticides for treating textiles, leather, and other organic materials. Horsfall [15] tested β-nitrostyrene and β-methyl-β-nitrostyrene and described them as excellent fungicides with reasonably good protective powers for foliage. Isoeugenol, which is a component of certain essential oils and the formula of which is *p*-hydroxy-*m*-methoxy-β-methylstyrene, was recently studied by Vilanova and Casanovas [16] as a fungistatic compound.

The present findings extend to pathogenic fungi. The studies of McGowan and associates [10] on the effectiveness of the nitrostyrenes were made with nonpathogenic species. We have noted the relative inactivity of the monomeric styrene. This was similarly observed by McGowan and his co-workers,[10] who listed the least effective concentrations of the various nitrostyrenes they examined as ranging from 0.8 to 16 γ per milliliter while those of styrene were listed as 400 to 500 γ per milliliter. They pointed out that the compounds they tested which showed the highest fungistasis had, attached to one of the double-bonded carbon atoms, a strongly electron-attracting group known to render adjacent methylene groups reactive and to have acidic hydroxyl derivatives whose acidity might be used as a convenient measure of

electron attraction. Hence, the authors claimed that, since nitric acid is a very strong acid, all compounds having the —C=C—NO_2 grouping are powerful fungicides. On the other hand, compounds with the group —COOR, —COR, —COOH, or —CHO attached to the ethylenic double bond have corresponding hydroxy compounds which are weak acids and therefore show less activity.

TABLE 4.—*Screening for Antifungal Activity of Certain Aromatic Ethylenes and Other Compounds: Lowest Effective Concentration in Mg./per Ml. Medium*

Compounds	Chemical Formulae	T. Rubrum	M. Audouini	C. Albicans	C. Neoformans	B. Dermatitidis
Dibenzoylethylene (trans)		0.01	0.01	>1.0	0.1	0.01
Dibenzoylethylene (cis)		0.01	0.01	>1.0	0.1	0.01
Benzalacetophenone		0.01	0.01	>1.0	0.1	<0.001
Dypnone		0.01	0.1	>1.0	>1.0	0.1
1,1-Bis-(*p*-methoxyphenyl)ethylene		>1.0	>1.0	>1.0	>1.0	>1.0
1,1-Bis-(*p*-methoxyphenyl)-2-phenylethylene		>1.0	>1.0	>1.0	>1.0	>1.0
1,1-Bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)ethylene		0.01	0.01	>1.0	>1.0	0.01
1,1-Bis-(*p*-propionoxyphenyl)-2-(*p*-methoxy-phenyl)-2-bromoethylene		>1.0	>1.0	>1.0	>1.0	>1.0
1,1-Bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)ethylene		>1.0	>1.0	>1.0	>1.0	>1.0
α,β-di-*p*-Methoxyphenylvaleric acid		1.0	>1.0	>1.0	>1.0	0.01
α,β-di-*p*-Methoxyphenyl)valeronitrile		>1.0	>1.0	>1.0	>1.0	>1.0
2,6-Dibenzalcyclohexanone		>1.0	>1.0	>1.0	>1.0	>1.0
9-Anisalfluorene		>1.0	>1.0	>1.0	>1.0	>1.0
2,4-Diphenylbicyclo-(3,3,1)-non-2-ene-9-one		>1.0	>1.0	>1.0	>1.0	1.0
Versenic acid (used as sodium salt)		1.0	>1.0	>1.0	>1.0	>1.0
Sorbic acid		1.0	0.1	1.0	1.0	1.0

The slight activity exhibited by β-bromostyrene was contrary to expectations in view of the often-made observation that the introduction of a halogen atom into the molecule of an organic compound increases its fungistatic activity. It may be interesting to determine the activity of halogenated nitrostyrenes with substitutions on the benzene ring and/or the ethylene carbon atoms.

IN VIVO STUDIES

Experiments were undertaken to determine if the nitrostyrenes are also active in vivo against experimental mycoses in laboratory animals. The desirability of these studies cannot be overemphasized, as it is well known that there are not a few compounds which are extremely active in the test tube against organisms and yet are inactive against infections in vivo. Furthermore, a compound may be active, but its high toxicity may preclude its use in humans as a chemotherapeutic agent.

TABLE 5.—*In Vitro Antifungal Activity of Certain Stilbenes and Aromatic Diamidines: Lowest Effective Concentration in Mg. of Drug per Ml. Medium*

Fungi	Stilbamidine Isethionate	2-Hydroxystilbamidine Isethionate	Aminostilbamidine HCL	Diethylstilbestrol	Propamidine Isethionate	Pentamidine Isethionate
Trichophyton mentagrophytes	1.0	1.0	1.0	0.1	1.0	1.0
Trichophyton rubrum	1.0	1.0	1.0	0.01	1.0	1.0
Trichophyton schoenleini	1.0	1.0	1.0	0.01	1.0	1.0
Trichophyton violaceum	1.0	1.0	1.0	0.01	1.0	1.0
Trichophyton ferrugineum	1.0	1.0	1.0	0.001	0.1	1.0
Trichophyton tonsurans	1.0	1.0	1.0	0.01	1.0	1.0
Microsporum gypseum	1.0	1.0	1.0	0.1	1.0	1.0
Microsporum audouini	1.0	1.0	1.0	0.1	1.0	1.0
Microsporum canis	1.0	1.0	1.0	0.1	1.0	1.0
Epidermophyton floccosum	1.0	1.0	1.0	0.01	1.0	1.0
Cladosporium werneckl	1.0	1.0	1.0	0.1	0.1	1.0
Hormodendrum pedrosoi	0.01	0.1	1.0	1.0	0.1	0.1
Phialophora verrucosa	1.0	...	...	1.0	0.1	1.0
Monosporium aplosperum	1.0	1.0	1.0	0.1	1.0	1.0
Nocardia asteroides	1.0	1.0	1.0	0.01	1.0	1.0
Candida albicans	1.0	1.0	1.0	1.0	1.0	1.0
Cryptococcus neoformans	1.0	1.0	1.0	1.0	1.0	1.0
Sporotrichum schenkii	1.0	1.0	1.0	1.0	0.01	0.001
Blastomyces dermatitidis	0.1	0.1	0.1	0.001	0.1	1.0
Blastomyces dermatitidis, 37 C	0.01	...	...	0.01	0.01	1.0
Blastomyces braziliensis	1.0	0.1	0.1	0.001	0.01	1.0
Blastomyces braziliensis, 37 C	1.0	...	...	0.01	0.1	0.1
Histoplasma capsulatum	1.0	1.0	1.0	0.001	1.0	1.0
Histoplasma capsulatum, 37 C	0.1	...	...	0.1	0.01	1.0
Coccidioides immitis	1.0	...	...	0.01	0.1	1.0
Alternaria sp.	0.1	1.0	1.0	1.0	0.01	1.0
Penicillium sp.	1.0	1.0	1.0	1.0	1.0	1.0
Aspergillus niger	1.0	1.0	1.0	1.0	1.0	1.0

The experimental organism chosen was B. dermatitidis. Mice were utilized, since they lend themselves well to protective experiments, and are readily available. Since nitrostyrenes are insoluble in water, one of the initial problems that arose was the choice of a suitable solvent which was relatively innocuous to the test animals. Acetone, which was used as the solvent in the in vitro experiments, was obviously unfit for animal administration. The compounds were found to be soluble in propylene glycol, olive oil, and peanut oil. Because of its wider clinical use as a solvent for water-insoluble drugs, propylene glycol was selected. The intraperitoneal route of administration was used because of its simplicity in small animals like mice. The quantity of propylene glycol to be injected per administration was arbitrarily set at 0.1 ml.

No adequate biological assay in animals of the nitrostyrenes has been done, and there is a dearth of data on their toxicity, effects on tissues and organs, and dosage levels. Brian, Grove, and McGowan [17] referred to β-nitrostyrene as a powerful sternutator and *p*-methoxy-β-nitrostyrene as a nonirritant on humans.

The M. L. D. and L. D_{50} of each drug used had to be determined before protection experiments could be undertaken with mice. The three drugs chosen for these experiments were dissolved in propylene glycol and injected intraperitoneally

TABLE 6.—*Antifungal Activity of Certain Styrenes: Lowest Effective Concentration in Mg. of Compound per Ml. Medium*

	Monomeric Styrene	β-Bromostyrene	β-Nitrostyrene	*p*-Methoxy-β-nitrostyrene	*p*-Acetoxy-β-nitrostyrene	β-Methyl-β-nitrostyrene	*p*-Methoxy-β-methyl-β-nitrostyrene	*o*-Methoxy-β-methyl-β-nitrostyrene
Trichophyton mentagrophytes	>1.0	>1.0	0.1	0.1	0.1	0.001	0.001	0.01
Trichophyton rubrum	>1.0	>1.0	0.01	0.01	0.01	0.001	0.001	0.01
Trichophyton schoenleini	>1.0	1.0	0.1	0.1	0.1	0.001	0.001	0.01
Trichophyton violaceum	>1.0	1.0	0.01	0.01	0.1	0.001	0.001	0.01
Trichophyton ferrugineum	>1.0	1.0	0.1	0.1	0.1	0.001	0.01	0.01
Trichophyton tonsurans	>1.0	>1.0	0.1	0.1	0.1	0.01	0.001	0.01
Microsporum gypseum	>1.0	>1.0	0.1	0.1	0.1	0.001	0.01	0.01
Microsporum audouini	>1.0	>1.0	0.001	0.01	0.01	0.001	0.001	0.01
Microsporum canis	>1.0	>1.0	0.1	0.1	0.1	0.001	0.01	0.01
Epidermophyton floccosum	>1.0	>1.0	0.1	0.1	0.1	0.001	0.001	0.01
Cladosporium wernicki	>1.0	>1.0	0.1	0.1	0.1	0.01	0.01	0.01
Hormodendrum pedrosoi	>1.0	>1.0	0.1	0.1	0.1	0.01	0.01	0.1
Monosporium apiospermum	>1.0	>1.0	0.1	0.1	0.1	0.01	0.001	0.01
Nocardia asteroides	>1.0	>1.0	>0.1	>0.1	0.1	0.1	0.1	0.1
Candida albicans	>1.0	>1.0	0.1	0.1	1.0	>0.1	0.1	0.1
Cryptococcus neoformans	>1.0	>1.0	0.01	0.01	0.1	0.001	0.01	0.1
Sporotrichum schenckii	>1.0	0.1	0.01	0.01	0.01	0.01	0.001	0.1
Blastomyces dermatitidis	>1.0	>1.0	0.001	0.01	0.01	0.001	0.001	0.001
Blastomyces braziliensis	>1.0	0.1	0.01	0.01	0.001	0.001	0.001	0.1
Histoplasma capsulatum	>1.0	>1.0	0.1	0.1	0.1	0.001	0.001	0.01
Alternaria sp.	>1.0	>1.0	>0.1	>0.1	>0.1	0.1	0.1	0.1
Penicillium sp.	>1.0	>1.0	>0.1	>0.1	>0.1	0.1	0.1	0.1
Aspergillus niger	.....	>1.0	>0.1	>0.1	>0.1	0.01	0.1	....

daily at different dosage levels. Ten mice were used for each experiment. The results of these experiments are as follows:

1. β-nitrostyrene — M. L. D.—25.0 mg. per kg. per 6 hours; L. D_{50}—22.5 mg. per kg. per 24 hours
2. β-methyl-β-nitrostyrene — M. L. D.—110.0 mg. per kg. per 6 hours; L. D_{50}—82 mg. per kg. per 20 hours
3. *p*-methoxy-β-methyl-β-nitrostyrene — M. L. D.—162.0 mg. per kg. per 24 hours; L. D_{50}—130.0 mg. per kg. per 24 hours

Following the assay of these three compounds, the experimental infection with B. dermatitidis in mice was achieved by following Heilman's technique.[18] B. dermatitidis was grown in its yeast form on Sabouraud's blood dextrose agar at 37 C. This was harvested and a 250 mg. per 100 cc. suspension in Ringer's solution was made. A count of the yeast-like blastomycetes in the suspension revealed a concentration in round figures of 1,000 organisms per cubic millimeter. One-tenth milliliter of

this suspension, equivalent to 100 organisms per cubic millimeter, was injected intravenously into the tail vein of each mouse. The average weight of the mice used was approximately 20.5 gm.

Since β-methyl-β-nitrostyrene was found, in vitro, to be the most effective drug it was used in the protective experiments. The compound was dissolved in propylene glycol and injected intraperitoneally every day in arbitrary doses of ½ and 1/10 of the L. D_{50} previously established as 82.0 mg. per kilogram. The injections of the drug were started four days after the intravenous inoculation of the animals with B. dermatitidis.

Animals that died were autopsied and the organs were examined for gross evidences of blastomycosis or other causes of death by smears, cultures, and histopathological sections.

The experimental data are shown in Table 7. It will be seen that in 13 days infected mice given intraperitoneal injections of propylene glycol only had a mortality rate of 80%. Only 20% of the infected control mice died during this period.

TABLE 7.—*Results of Protective Experiments Against Blastomycosis in Mice Using β-Methyl-β-Nitrostyrene in Propylene Glycol*

		No. Deaths						
							Total	
	No. Mice	1st Day	2d Day	3d Day	4th Day	13th Day	No.	%
Uninfected animals injected with Ringer's solution	10	0	0	0	0	0	0	0
Uninfected animals injected with propylene glycol	10	0	0	0	0	1	1	10
Infected controls	10	0	0	0	0	2	2	20
Infected animals injected with propylene glycol	10	2	0	0	0	6	8	80
Infected animals injected with ½ LD_{50} of drug in propylene glycol	15	7	5	3	0	15	15	100
Infected animals injected with 1/10 LD_{50} of drug in propylene glycol	15	1	1	1	1	9	13	86.6

Uninfected mice given the same number of injections of propylene glycol had only a 10% mortality. No death occurred in the uninfected group given intraperitoneal injections of Ringer's solution. One hundred per cent of the infected mice treated with one-half of the L. D_{50} dose of β-methyl-β-nitrostyrene died in the third day while 86.6% of those treated with one-tenth L. D_{50} of the same drug died in 13 days. The toxic effect of propylene glycol was enhanced by the incorporation of β-methyl-β-nitrostyrene. As a solvent for drugs, propylene glycol is widely used and considered essentially nontoxic.‡ Our data shows it to be highly toxic when given with both B. dermatitidis and β-methyl-β-nitrostyrene. Karel, Landing, and Harvey [22] similarily studied the acute, intraperitoneal L. D_{50} in mice of 16 solvents belonging to the glycol, glycol ether, glycol ester, and pthalate series. They found the value for propylene glycol as 127.87 mM. per kilogram, or 9.36 ml. per kilogram of body weight. In their discussion they stated that any pure solvent, regardless of its inherent toxicity, introduces a hypertonic solution which may in itself lower the resistance of the host and potentiate the toxic action of the compound being assayed.

A similar phenomenon, called "virulence enhancement," was observed by Seligmann § in C. albicans infections when antibiotics of the chlortetracycline (Aureo-

‡ References 19 to 21.

§ References 23 and 24.

mycin) and oxytetracycline (Terramycin) groups were used. He found that suspensions of C. albicans were nonpathogenic and solutions of chlortetracycline and/or oxytetracycline nontoxic when either alone was injected intraperitoneally in mice. However, the injection of a combination of the yeast and either antibiotic proved fatal. Seligmann attributed this "virulence enhancement" of C. albicans by chlortetracycline and/or oxytetracycline to a lowered resistance of the animal host to infection.

In view of our adverse results with propylene glycol as a vehicle, other carriers had to be considered. Another experiment was undertaken, using the drug suspended in microcrystalline form in Merck vehicle. The latter has the following formula:

	Gm. or Ml.
Sodium carbomethylcellulose	1.0
Sodium chloride	1.8
Benzyl alcohol	3.0
Sorethytan (20) monooleate (Tween 80)	0.8
Injectable water, q.s. ad	200.0

TABLE 8.—*Results of Protective Experiments Against Blastomycosis in Mice Using β-Methyl-β-Nitrostyrene in Merck Vehicle*

	10 Daily Injections					20 Daily Injections			
		No. Deaths					No. Deaths		
	No. Mice	0-19 Days	20-26 Days	27-40 Days	Total	No. Mice	0-19 Days	20-26 Days	Total
Infected controls	5	2	2	0	4	..	..	..	..
Uninfected animals treated with Merck vehicle	5	0	0	0	0	..	..	..	..
Infected animals treated with Merck vehicle	5	1	0	1	2	..	..	..	..
Infected animals treated with 50% LD_{50} of drug in Merck vehicle	3	0	0	1	1	4	0	4	4
Infected animals treated with 10% LD_{50} of drug in Merck vehicle	3	0	0	1	1	4	0	4	4
Infected animals treated with stilbamidine, 25 mg./kg.	5	0	0	0	0	..	..	..	..

Instead of waiting four days, as was done previously, we started the intraperitoneal injections of β-methyl-β-nitrostyrene suspended in Merck vehicle on the same day as the intravenous inoculum of 100 organisms of B. dermatitidis was given.

The results are shown in Table 8. This experiment was also preliminary in nature and the number of animals was small. Stilbamidine in a dose of 25 mg. per kilogram of body weight afforded the mice protection against blastomycosis, confirming the results of Heilman.[18] The results with β-methyl-β-nitrostyrene were inconclusive in view of the survival of three out of five infected mice treated alone with Merck vehicle. The surviving mice were ill, however, at the end of the experiment. The infected mice treated with β-methyl-β-nitrostyrene that survived, remained as healthy as the stilbamidine animals. The mortality of the infected mice, given 20 daily intraperitoneal injections of the drug, may have been caused by the cumulative toxic effect of the drug, by infection, or trauma.

It was also believed the number of organisms introduced into the mice might have been great enough to cause a fulminating, massive infection, overwhelming any protective action of the drug being examined. Thus, a preliminary biotitration to determine approximately the least number of organisms that causes 100% mortality was performed. Groups of five mice each were injected intravenously with 100 organisms per mouse in the first group, 50 in the second, and 25 in the third. It was found that 100% mortality occurred with the injection of even 25 organisms of B. dermatitidis per mouse.

These experiments are to be repeated and extended.

SUMMARY

The antifungal activity of a large number of compounds structurally related to the stilbenes is reported.

These compounds, including a number of cinnamic acid derivatives and aromatic ethylenes, were screened by means of the serial dilution agar method. Their activities varied and the nitrostyrene group, particularly β-methyl-β-nitrostyrene and p-methoxy-β-methyl-β-nitrostyrene, were highly potent.

The nitroethylene radical —C=C—NO_2 seemed most important in this antifungal activity.

M. L. D. and L. $D._{50}$ determinations of β-nitrostyrene, β-methyl-β-nitrostyrene, were done. The latter two compounds had an L. $D._{50}$ of 82 and 130 mg. per kilogram in 20 and 24 hours, respectively.

Preliminary animal protective experiments against B. dermatitidis in mice using β-methyl β-nitrostyrene are reported.

An additional finding in these experiments was the toxicity of propylene glycol when injected intraperitoneally into B. dermatitidis infected mice.

ABSTRACT OF DISCUSSION

DR. MAURICE SULLIVAN, Baltimore: On Wednesday, Dr. Kligman described the mechanism of infection of the scalp by M. audouini and M. canis. He emphasized the superficial nature of fungus infections of the skin and their resistance to antifungal agents in spite of the fact that the infective agent is harbored in easily accessible tissue. The persistence of superficial fungus infection has always bewildered dermatologic therapists, and 100 years of research have not produced a satisfactory fungicide. The quest for antifungal drugs continues to be one of the most elusive problems in experimental and clinical dermatology.

For the past five years, our group and several others have tested thousands of new antifungal compounds and have not found one that is satisfactory. The introduction of stilbamidine and diethylstilbesterol for the treatment of blastomycosis seemed to offer hope of a new approach. We had anticipated the use of these drugs for the dermatomycoses but they have not been applicable because, as Dr. Curtis and his co-workers have stated, there are shortcomings to the use of stilbamidine and diethylstilbesterol. They are searching for suitable, structurally related compounds, and it is hoped that they will discover less toxic drugs.

Recently, 2-hydroxystilbamidine has been used in extensive clinical trials. It has been claimed that 2-hydroxystilbamidine is as effective clinically as stilbamidine but that it is less toxic. As it is a more stable compound than stilbamidine it would be a more suitable drug for clinical evaluation than stilbamidine. It is obvious that much animal investigation and extensive toxicity tests must be performed before these drugs can be tested clinically in the superficial mycoses.

We recently initiated a pilot experiment to investigate 2-hydroxystilbamidine for the treatment of tinea capitis due to M. audouini. We terminated the experiment after we had treated two children because we were informed that there were instances of fifth nerve involvement in patients elsewhere who had been treated with dihydroxystilbamidine. This was a very exciting experiment when it was undertaken, because we were under the impression that dihydroxy-

stilbamidine was not toxic and also because dihydroxystilbamidine, or evidence of it, was manifested by red fluorescence on the scalp and in the hair while it was being taken. The two children we treated showed, intermingled with the numerous shiny green hairs, areas of dusky redness, indicating the presence of the drug or of a product of the drug. However, neither one of these children showed any clinical improvement, in spite of the fact that we were convinced that the drug or a product of the drug was being delivered to the spot where it was desired.

We have recognized, and Dr. Sulzberger's group and the other groups working with the Surgeon General have recognized, the necessity for suitable test animals to be utilized for experiments such as Dr. Curtis and his group are performing, and at present we are concentrating our efforts on technics for producing fungus infections in small laboratory animals. This problem is one of great magnitude, and until we solve it progress in the testing of fungicides will be impeded. Dr. Wood, in our laboratory, has spent two years trying to standardize on a quantitative basis C. albicans infection in mice.

Dr. Curtis has recited to us just a few difficulties in this tremendous piece of work he has done. The use of a solvent in test animals is only one of the numerous bewildering situations that arise in the fungicide testing business. The testing of antibacterial drugs is a comparitively easy matter consisting of injecting drugs into test animals with standardized infections. We are far from perfecting similar procedures for testing fungicides in laboratory animals infected with fungi.

Dr. Curtis and his group are to be commended and congratulated on this great piece of experimental work in a difficult field.

Dr. J. Walter Wilson, Los Angeles: I, who live in Hollywood, do not consider myself appropriately selected to discuss this paper, since I cannot express my opinion of it adequately without using those superlatives, such as "stupendous," "gigantic," "colossal," and "terrific," which, by being associated for so long with mediocre celluloid products from my locality, have lost their descriptive powers. I hope it will suffice to state that in this paper, Drs. Curtis, Bocobo, Harrell, and Block have made another in a series of splendid contributions toward the control of fungus infections.

It is nothing new for me to say that the treatment of the mycoses will not be entirely successful until we are able, by the systemic administration of a therapeutic agent, to confer upon every cell in the animal body the power to resist or kill fungi. That this is true of the deep mycoses is obvious, but I consider it equally applicable to the tineas as well, since we are not handicapped in their treatment because of our lack of potent antifungal agents, but because we cannot by external application cause them to penetrate as deep as do the invading fungi. We need agencies which act from within outward, and I congratulate Dr. Curtis and his group on having the courage to attack a problem so necessary to our advancement.

The principal difficulty lies in the overwhelming size of such a research project. For example, here is reported a screening process involving 55 chemicals—a very large number, to be sure, representing a huge amount of work. However, a hundred such studies will be necessary to duplicate the chemical investigations which followed closely upon the advent of sulfanilamide, in which several thousand related compounds were tested, of which less than 10 survive today.

Also, there are many pitfalls in the course of such studies as these. One which concerns me is the degree to which in vitro studies are relied upon. It is by now trite to say that in vitro antifungal activity does not indicate clinical effectiveness against fungus disease. How accurate, then, is the corollary, the assumption that we may eliminate from further consideration all substances which do not exhibit antifungal potency in vitro? For this to be true, we must postulate that all such substances retain their integrity during all their stay in the animal body; that they do not become associated with other substances, and that they are excreted entirely unchanged from the form in which they were injected. Instead, many of them will certainly be degraded, conjugated, precipated, localized, or otherwise altered after they are administered. It may well be that a substance originally entirely inactive in vitro will thus be converted into an effective therapeutic agent. There are also defects in animal experimentation, since a mechanism which works well in one species may fail utterly in another.

Particularly discouraging is the outlook from the antibiotic aspect. Literally, the soils of the world have been screened in search of these substances. For several years continuously an average of more than 200 new specimens weekly in one institution alone have been obtained from

farms and rivers, mountain tops and glaciers, deep sea dredgings, the tombs of mummies, and the centers of frozen dinosaur eggs, and still we do not possess an antifungal antibiotic sufficiently nontoxic for adminstration to human beings.

Thus, although the way is clear, it is likely to be very long. Let nothing I have said detract from such reports as these which we have heard today, which are laudable steps in the right direction.

DR. ARTHUR C. CURTIS, Ann Arbor, Mich.: I wish to thank Dr. Sullivan and Dr. Wilson for their discussion.

Apropos of what Dr. Sullivan said about 2-hydroxystilbamidine, one patient with pulmonary blastomycosis, who relapsed five times (his relapses had been relatively minor compared to the severity of his disease in the begining), has an in vitro resistance of his organisms to the stilbenes. On one occasion, during these five retreatments, he was given 2-hydroxystilbamidine. Within a course of about five days, he developed a very severe agranulocytosis. The drug was stopped, and within a short time he recovered. We have not used it in his case since.

Hydroxystilbamidine is apt to be almost as toxic as stilbamidine.

I appreciate, as does Dr. Wilson, that one cannot apply in vitro experiments to human beings. Sometime ago we were interested in a simple acetic acid compound which, in the test tube, worked beautifully; yet when we gave it to the human being, it was conjugated in the liver, made into a harmless compound, and had absolutely no effect on the diseases in which we were using it.

The organic chemists have told us that from the structure of the nitrostyrene group they should be able to be given by mouth. The in vivo experiments are being pursued diligently and further studies will be reported later.

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CARDIOVASCULAR SYSTEM SYPHILIS

Observations on Patients Treated Over Five Years Ago With 4,008,000 Units of Penicillin

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PENICILLIN therapy of cardiovascular system syphilis has been reported to be efficacious and relatively free from undesirable side-reactions by many observers.* Unfortunately, most of the reports limit the period of observation to a few months rather than years and make no clear comparison between patients treated with either heavy metals or arsenic and those treated with antibiotics like penicillin. Padget and his group † attempted such a study and, after analyzing 1,020 cases treated by various methods and drugs, concluded that individual variation, methods of diagnosis, and systems of case recording made it difficult to appraise therapy. However, they were able to gather sufficient information to state that women had a better prognosis than men, and white patients better than nonwhite. In a similar review of 334 cases, Barnell and Small found that penicillin favorably influenced the prognosis of any type of cardiovascular syphilis and that it was more effective when given before cardiac symptoms had appeared.

In 1951, we [5] reported 17 cases of cardiovascular syphilis treated with 4,008,000 units of aqueous penicillin G given intramuscularly on a schedule of gradually increasing dosage. After following some of the patients for 991 days, we concluded that penicillin was valuable in the treatment of the disease. This conclusion was based on subjective betterment as well as improvement shown in the electrocardiogram, the orthodiagram, the roentgenogram, and the serologic trend of the blood and spinal fluid in most of the patients. The present report surveys the original 17 patients and 2 additional patients some 85 months after treatment to see whether penicillin arrested the progression of cardiac syphilis.

It will be noted that 10 of the 19 patients have died; they lived an average of 25 months after treatment and 64 months after the onset of symptoms or the time of diagnosis. Five patients who died had aortic aneurysms; they lived on the average of 23.5 months after treatment and 53 months after the onset of symptoms. All four patients with aortic insufficiency died on the average of 22 months after penicillin administration and 74 months after the appearance of symptoms. One

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* References 1 through 8.

† References 9 through 11.

patient with combined aortic aneurysms and aortic insufficiency died 44 months after receiving medication and 74 months following the onset of his illness.

On comparing Moore's ‡ results with ours in patients with aortic aneurysm who have died, it is noted that his therapy of heavy metals and arsenic seems to have given a better survival rate than ours with penicillin—74 months to 53 months. Since four of our patients with aneurysms are still living, the survival figure may still equal that of Moore's. The survival period in our patients with aortic insufficiency who died compares closely with Moore's—74 months to 75 months. Our series of cases is small, but the figures at present suggest that penicillin may not be any more efficient than the heavy metals reported by Moore in 1941 and 1949 in the treatment for aortic aneurysm and aortic insufficiency.

Of the patients still living, several have been followed for 85 months after therapy, and the average for all the living ones is 70 months. Four patients with aortic aneurysm have been observed for an average of 66 months after therapy. Symptoms of cardiac syphilis have been present in this group for an average of 80 months. Three cases of aortitis have been followed for an average of 78 months after treatment was instituted with penicillin. The average time for symptoms to be present in this group was 90 months. The two surviving patients with combined aortic insufficiency and aneurysm have been followed for an average of 65 months after treatment. The condition was diagnosed or symptoms have been present on the average of 107 months.

Only 3 of the 19 patients were asymptomatic at the time therapy was begun, and these three are enjoying good health on an average of 75 months after therapy. Two patients—one with combined insufficiency and aneurysm and the other with aneurysm—have become worse according to the orthodiagram, roentgenogram, and electrocardiogram studies. One of these has received an additional 4,000,000 units of penicillin and the other 6,000,000 units. In one instance, additional penicillin was given because of sustained symptoms of central nervous system syphilis and not because of progression of cardiac syphilis.

Of the 11 patients with positive spinal fluid changes indicating syphilis, 6 are still living, and in 3 of these a positive spinal fluid reaction was favorably influenced by penicillin but not eradicated. Persistence of positive spinal fluid findings is not unusual, according to Thomas [16] who stated that 65% of adequately treated patients will still have spinal fluid reagins five years after therapy.

We have previously shown that the electrocardiogram gives no pattern which is pathognomonic of cardiovascular syphilis except for changes which go with left ventricular strain due to aortic insufficiency or changes due to coronary involvement. In the electrocardiogram of nine living patients, there has been no change in four, improvement in one, and progression in three as evidenced primarily by left ventricular hypertrophy. This electrocardiographic change alone does not indicate an unfavorable prognosis.

The roentgenograms of four living patients show progressive ventricular hypertrophy, which is not a significant finding in this age group with aortic insufficiency and hypertension.

In reviewing certain factors in individual cases, one finds that the presence of hypertension and cardiac syphilis did not shorten patients' lives. For instance, one

‡ References 13 and 14.

patient has had a known hypertension of over 200 mm. of mercury for at least seven years. Wide pulse pressures have been present in three cases for at least five years. Similar changes were seen in four other patients who have died. It would appear, then, that wide pulse pressure does not alter a patient's prognosis.

The average age at the time of initial penicillin treatment in patients still living and in those who have died was essentially the same.

Our original impression that the orthodiagram was valuable in prognosticating fatalities remains unchanged. In the 10 patients who died, the orthodiagram showed poor prognosis in 6 and good in only 1. Of the nine living patients, two showed unfavorable orthodiagram changes five years ago; today, four have shown no change, and the rest generally have shown progression of the disease.

After the various procedures used to study the cardiac status of the patients are reviewed, it appears that the functional capacity best indicates the prognosis. In fact, all patients who had a functional capacity of III and approximately one-half of those with a functional capacity of II have died. All patients with a functional capacity of I are still living. In two cases, there is improved functional capacity; and in two it is worse. Among the present living patients, there is none with a functional capacity of III.

COMMENT AND SUMMARY

The great difficulty in evaluating therapy in cardiovascular syphilis cited by others is supported in our evaluation of 19 cases treated five years ago with 4,008,000 units of penicillin. It appears that the results of penicillin therapy are no better than in those patients treated with adequate amounts of heavy metals or arsenic. Although 4,008,000 units of penicillin appeared to be an adequate dose in the majority of living patients, progression of cardiovascular changes occurred in two. It is felt that larger doses, perhaps 9,000,000 to 10,000,000 units, might be better. The orthodiagram continues to be an important prognostic procedure. Patients were observed to remain well and active with marked hypertension, wide pulse pressure, and severe electrocardiographic and roentgenographic changes. When cardiac symptoms indicated a classification of functional capacity III, the prognosis was poor.

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BANK CHECK DERMATITIS

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THE CONTACTANTS known to produce allergic eczematous contact dermatitis are almost innumerable, but one commonplace article apparently unrecognized as a possible cause of skin eruptions is the bank check. Considering the vast number of exposures to checks, I believe the occurrence of contact dermatitis from them to be worthy of note.

REPORT OF CASES

CASE 1.—N. L., a white woman, aged 52, presented a subacute eczematous dermatitis on the dorsum of the fingers and hands, forearms, face, and neck.

She stated that the eruption was of four years' duration, that there had been numerous exacerbations and remissions, that these flare-ups occurred at weekly intervals, usually on Thursday and Friday, partially subsiding during the remainder of the week, and that Thursday and Friday were the days on which as a bookkeeper she prepared a weekly payroll. She had been an employee of the same firm for seven years, performing the same type of work. A diagnosis of neurodermatitis had been made earlier because the eruption worsened on the days when she was under the nervous tension of preparing the company pay checks.

A series of patch tests with suspected allergens were applied, and a positive (2+) reaction was obtained solely from the bank checks with which she worked. The dermatitis disappeared promptly with local treatment and avoidance of the checks. By wearing cotton gloves she then managed to continue at the same job, handling the same checks, with only a minimal amount of discomfort.

CASE 2.—B. A., a white woman, aged 44, presented an acute eczematous dermatitis on the dorsum of both hands and on the wrists. The eruption had begun on the side of the right palm and fifth finger where one rests the hand in writing. The duration of the disease was three weeks. The patient was the payroll clerk for a large industrial firm where she had been employed for several years. Her major duty was to prepare the pay checks. (Significantly these checks were manufactured by the same company as in Case 1.) There had been no recent changes in the type of check used.

Patch tests were applied with these bank checks and a positive reaction was obtained. The patient was also patch-tested with the checks from Case 1, to which she gave a negative reaction. The two checks were of a different color, which would indicate that the allergen was possibly a dye.

Local treatment and subsequent avoidance of the checks resulted in improvement of the dermatitis.

COMMENT

The bank checks causing the dermatitis in the two patients cited were of the "safety type" bank check, as are the great majority of all bank checks in use today. A safety check contains a coating of ink to prevent alterations and forgery; e. g.,

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the application of ink eradicator to its surface produces a visible discoloration. A special feature of the checks producing the dermatitis was the appearance of the word "void" in red after the application of ink eradicator.

The ingredients of ink are each manufacturer's trade secret. A request to the manufacturer of the checks for samples of the chemical components of their ink was refused because of the "great number and complexity of the chemicals involved." Thus, it was not possible to determine by patch testing the irritating chemical or chemicals in the ink.

However, the chemist for the check company did provide some general information regarding the composition of their inks. The following chemicals or types of chemicals would be found in the processing and printing ink on one of this company's bank checks: maleic acid-rosin condensate resin, phenolic resins, alkyd resins, inorganic dyes, organic dyes, fluorescent pigments of the zinc and cadmium sulfate class, cobalt, manganese, lead, diethylene glycol, and linseed oil. The presence of a number of resins and dyes in the ink capable of causing contact dermatitis may be noted.

The scarcity of reports in the literature on contact dermatitis from ink in the dry state would indicate that it is not a common occurrence. One report by Oliver [1] in 1928 records several cases of contact dermatitis due to a red dye, para-red, in the ink of the newspaper rotogravure section. The ink on carbon paper [2] has been noted occasionally also to produce contact dermatitis, but Schwartz and Sulzberger [3] were unable to find any cases proved by patch test. These authors concluded that dermatitis from carbon paper is exceedingly rare. I failed to find any reports of contact dermatitis due to bank checks.

SUMMARY

Two cases of allergic eczematous contact dermatitis from the ink in bank checks proved by patch test are described. A great number of chemicals are contained in the ink coating on safety-type bank checks. Many of them are known sensitizers, but because of the very nature of being in the ink in bound form as well as in the dry state, it is probable that dermatitis from them in the finished state is not common.*

* Birmingham, D. J.: Personal communication to the author.

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SCHISTOSOME DERMATITIS

Report of an Outbreak of "Swimmers' Itch"

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FIFTY-THREE picnickers, affected in this outbreak, were members of a small community, and available for early examination, and follow-up.

The natural history of the condition, which was first described by Cort [1] from Michigan, is briefly as follows: Cercariae pass from snail to fish; the fish is eaten by a bird and the organism reenters the lakewater from the birds' droppings. Cercariae from the snail may infest man instead of fish and give rise to a skin eruption; man is an unsatisfactory host, and the cercaria dies after penetrating the human epidermis.

Eighty-eight persons bathed in Lake Nipissing, Ontario on June 20, 1953; 63 were under the age of 10 years.

SKIN MANIFESTATIONS

Early Manifestations.—Forty-five persons started itching at times ranging between 10 minutes and three hours after leaving the water. Seven persons stated that they started itching while in the water and one person did not notice itching until the following day. Most of the cases were observed during the first half-hour after itching started. In many cases there were no lesions visible on the skin, while in others wheals were visible. Children soon produced excoriations on clinically normal skin or on wheals. Children with severe itching ran and danced about and some became difficult to manage. The itching appeared to be constant rather than paroxysmal; it appeared to reach a height of intensity in half an hour and gradually subsided.

Twenty-one persons suffered itching for less than 6 hours and five for about 24 hours. The itching was worsened by warmth, and sleeplessness was common on the first night.

Late Manifestations.—Twenty-two persons itched for longer than 24 hours; of these, 18 itched for periods up to six days. Four persons itched for longer than seven days.

In most cases the wheals subsided in a few hours. Bright red macules appeared on the skin and became papular overnight. Vesiculation occurred in some papules, but most were altered by scratching, and a few pustules were seen.

During the second and third days the papules became a darker red color and flattened. Unscratched papules faded by the end of a week, leaving nor-

From Royal Canadian Air Force Hospital, Rockcliffe, Ottawa. Biopsy study by Dr. H. J. Barrie, Department of Pathology, University of Toronto. Identification of snail by Dr. L. S. Russell, National Museum of Canada, Ottawa.

mal skin; after excoriation, bilirubin staining was visible for a longer period. Except where altered by scratching or secondary infection, all the lesions in these cases were uniformly in the same stage of development at a given time. The lower extremities and trunk were most affected: several patients had 200 or 300 papules on each lower extremity in uniform distribution: no papules were seen on the face, palms, and soles. The bathing trunk area tended to be spared; in some cases this area was scantily affected, though the upper abdomen and legs showed many lesions; there was a clear zone of skin corresponding to the belt.

INVESTIGATION

Snails were obtained from submerged rocks on the lake shore at the site of the picnic, on the following day. They were rinsed and placed in jars of tap water. The next day the water in the jars was found to contain large numbers of actively motile cercariae just visible to the naked eye; they were distributed equally through the water and did not tend to concentrate near the surface nor at the lighted side of the jar. If the snails were removed, rinsed again, and replaced in fresh tap water, a further batch of cercariae appeared on the next day.

Under the microscope these cercariae had the general appearance of those described as causing schistosome dermatitis. Each was actively motile, with a cylindrical body and a forked tail. If the water on the slide was allowed to dry, the cercaria under observation would shed its tail, which soon became immobile; the body continued in movement for a longer period.

A snail was identified as Stagnicola catascopium (Say).

Biopsy.—Two patients were subjected to biopsy, both at 44 hours after infestation; a well-marked papule was chosen for excision. The report submitted was as follows:

> Male, age 29. Skin from abdominal wall just above umbilicus.
>
> Male, age 29. Skin from thigh.
>
> Both biopsies were alike. The epidermis was normal except for isolated cells which were prominent because of pericellular or perinuclear edema. There was no edema of the papillae. The venules of the papillae showed slight hypertrophy of the endothelium and this was more pronounced the deeper they became. In the neighborhood of some of the sebaceous glands a few of them were reduced to solid cords. They, the arterioles and the small nerves were surrounded by a cellular exudate consisting of lymphocytes, small histiocytes and a few polymorphs and eosinophiles. Superficially this was slight, but, the deeper the vessels, the more marked was the exudate until it constituted a broad band at the level of the sebaceous glands. Some of the sebaceous glands were normal but in each biopsy one of them showed severe inflammatory cellular infiltration of a segment of their wall. The central sebaceous cells were not disturbed and appeared normal. No parasites were seen. There was little exudate around the sweat glands. These findings raise the question as to whether the portal of entry of the cercaria may have been the sebaceous gland.

Attempts at Experimental Infestation.—Attempts were made to infest three volunteers on two successive days. Drops of water containing one or two cercariae were allowed to dry on the skin of one forearm while lake water containing numerous other organisms but no cercariae was allowed to dry on the skin of the other forearm. No itching or eruption followed in any case; this point will be referred to in the comment.

COMMENT

Man is an unsuitable alternative to the fish as a host for the cercariae responsible for swimmers' itch. This probably explains the fact that man is not invaded by cercariae while bathing in the lake water; it is only when drops of water begin to dry on the bathers' skin that this species is driven to attempt infestation. It has been noted by several writers that prompt drying of the body after leaving the water prevents the condition. This did not appear at first sight to be supported by the figures relating to this outbreak. Over a third of the persons affected stated that they dried themselves; however, the air was balmy, and a light warm rain was falling, and its is thought that not many bothered to dry themselves completely. It is considered that bathers who are exposed to infestation should be recommended to dry promptly after leaving the water.

The great variation in the clinical course of the illness can be explained only on the basis of differences in host reaction: some persons who had numerous itching spots were hardly troubled at all after 12 hours, while others were in torment for a week. Olivier [2] as the result of a careful study, concluded that the reaction in the skin of man to cercariae of nonhuman schistosomes is essentially a sensitization phenomenon. He found that 33 of 34 persons exposed for the first time to cercariae had only mild, innocuous, and inconspicuous lesions; when 2/ of those persons were given from two to eight exposures to the same species, the reactions in most cases became progressively stronger, and 21 had eventually typical schistosome dermatitis. Olivier's conclusions, which are fully supported by the evidence given in his paper, appear to be at variance with the figures in this study, in which only 9 of 46 persons affected stated that they had had swimmers' itch before. It must be presumed that 37 had not noticed, or had forgotten, the sensitizing infestation. Certain persons appear to be refractory to infestation. Cort [1] noted that two of seven volunteers did not experience any effects whatever from repeated application of numerous cercariae to the skin, while application of a few of the same batch of cercariae caused lesions on his own wrist at each attempt. It is believed that the three volunteers chosen for attempts at experimental infestation in the present study were unlikely by reason of residence and habits to have been previously infested. It is suggested that this factor or refractoriness was responsible for the failure to produce lesions.

The time spent in the water did not seem to be related to infestation; 16 persons who spent 20 minutes or more in the water were unaffected. It was not discovered whether these persons were continuously immersed, while persons affected were running in and out of the water and thus were more often exposed to the effects of drying. Another factor which might explain why some were affected and some were unaffected, is the probability that the cercariae were not evenly distributed through the water but were present in swarms in proximity to the snails from which they had escaped. On the other hand, it is known that some cercariae tend to leave the snail in the early morning; by the afternoon, they would be expected to have dispersed; they would have been aided in dispersal by the waves produced by the gusty wind; they might, even so, be expected to congregate in an environment where light, temperature, depth, and oxygen content of the water suited them. To sum up, in addition to the factor of individual susceptibility, it is probable that some persons encountered water containing cercariae while others were more fortunate.

Statements are sometimes made locally that females are more often affected than males. This is not supported by these figures, since 27 males and 26 females were affected. As dark-haired persons have as a rule a more oily skin than fair-haired persons, it was suggested that a dark-haired person's richer sebum barrier might provide increased protection, but the figures obtained do not support this view.

It is possible that the feet were spared in this outbreak because the soft fine sand of the lake shore took up water drops immediately after the bather left the water. There was good evidence that bathing suits offered protection to the underlying skin, and the belt area was especially spared: the most popular suit worn was a close-meshed nylon suit which is relatively impermeable to water. The face was probably spared because it was rarely immersed, there being no diving points available.

Only 2 out of 15 paddlers were affected: this suggests that the cercariae do not prefer the shallowest water.

While observing the large numbers of children dancing and jumping about, I was vividly reminded of the dancing madness of the Middle Ages. It is not suggested, though, that this condition could explain some of the old epidemics, because it is likely that some mention of the prominent itching would have appeared in the descriptions.

No light was thrown on treatment by the study. The condition is unpredictable; sites where swimmers' itch is known to occur may be visited with impunity on some days but not on others. This particular picnic spot was visited by a large group of bathers on the day following the picnic described, and it is believed that not one of them was affected. Apart from pretreatment of the water with molluscicidal chemicals, such as copper sulfate, the only prevention that appears to be satisfactory at the present time is avoidance of bathing. The party involved here was warned not to swim after the first few cases occurred. The differences in incidence from day to day would appear to depend on meteorological or local water conditions.

Trout Lake, which is a few miles from Lake Nipissing, has been held responsible for cases of swimmers' itch for many years. Only in recent years have local physicians noted cases of infestation in Lake Nipissing. The cause of the spread of the organism, which is unknown, is of some importance to the tourist trade.

SUMMARY

The natural history of schistosome dermatitis is described from observation of 53 cases infested on the same day.

There is a striking variability in the clinical course which can be due only to differences in host reaction and is probably attributable to the phenomena of sensitization.

The effects of sex, of type and duration of immersion, and of drying, and the distribution of the eruption are discussed.

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Clinical Notes, New Instruments and Techniques

TWO TREATMENT FAILURES USING DIETHYLSTILBESTROL IN TREATMENT OF COCCIDIOIDOMYCOSIS

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Diethylstilbestrol has been used successfully by Curtis and Harrell [1] in the treatment of two cases of blastomycoses. The rationale for using female hormones for the treatment of deep mycoses is (*a*) the low incidence of deep mycoses in females, and (*b*) the in vitro fungistatic activity of these hormones. Bocobo, Curtis, and Harrell [2] reported excellent results on the in vitro fungistatic activity of diethylstilbestrol on Coccidioides immitis.

These two cases of coccidioidomycosis which were treated with large doses of diethylstilbestrol are reported because of the effects from administering 100 mg. per day for relatively long periods and the failure of this hormone in altering the disease.

REPORT OF CASES

CASE 1.—A 25-year-old Negro (Fig. 1) was stationed at Fort Bliss, El Paso, Texas, for one year. During that time he was on maneuvers in desert-like areas. In July, 1951, he was transferred to Germany. In August, 1951, he developed a pruritic pustule on the right ala nasi, which was excoriated and then crusted. In spite of treatment with various antibiotic ointments, the number of pustules increased so that a few pustules appeared on the mucosal surface of the right ala. The biopsy was positive for C. immitis, and the patient was transferred to Walter Reed Army Hospital. In November, 1952, there developed an indurated edema of the right side of the upper lip and right cheek, and at the same time a few vesicopustular lesions appeared in this same area.

Laboratory Findings.—The coccidioidin skin test was performed three times—before, during, and after treatment—and was positive in a dilution of 1:1,000. The complement fixation test for C. immitis was 1:64 when repeated at six-week intervals.

The battery of serological tests for syphilis and the first strength tuberculin test (1:100,000) were negative.

The white blood cell count was 7,800, with 61% neutrophiles, 34% lymphocytes, 4% monocytes, and 1% eosinophiles. The red blood cell count was 4,500,000, with a hemoglobin of 12.8 gm. The urinalysis was negative. The sedimentation rate was normal. X-rays of the chest and bony skeleton were negative. The 17-ketosteroids were 19 mg. per 24 hours. The sperm count was 7,000,000 per square centimeter three months after therapy was discontinued. There were no abnormal sperms. Unfortunately, sperm counts were not performed before initiating therapy.

Hospital Course.—The patient was given 100 mg. of diethylstilbestrol by intramuscular injection daily for 63 days. At the end of 63 days, the breasts did not increase any more in size nor was the pain any severer than after much smaller doses. The patient had relatively no decrease in libido during or after treatment. After the drug was discontinued, the gynecomastia began to subside in two weeks, and the breasts were normal in size in two months. There was no clearing of the granulomatous lesions on the ala or the cheek.

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CASE 2.—A 24-year-old Negro (Figs. 3 and 4), while training at Camp Desert Rock, Nev., in February, 1953, developed a cough and expectorated a white mucoid material. The cough was treated with acetylsalicylic acid and cleared in one week. He was apparently well until the middle of March, 1953, when he began to cough and expectorate some white mucoid material. The cough disappeared in four days, but he noted a subcutaneous nodule over the right

Fig. 1.—Coccidioidal granuloma of right ala nasi, right cheek, and lip. (Armed Forces Institute of Pathology #53-15361-A Ainst 13127-A.)

Fig. 2.—Coccidioidal granuloma of right clavicular area. (Armed Forces Institute of Pathology #53-20314-A Ainst 13464-A.)

clavicle and pain beneath both scapulae. The nodule became tender in a few days. The nodule was excised and evacuated of yellow purulent tenacious fluid. The site of excision, which was 2 in. (5 cm.) in length, continued to drain. Four weeks after the original nodule formed, the patient developed nodules on both flanks of the abdomen and on the right thigh. These nodules began to drain in two months. The patient experienced slight pain in the nodules before they

began to drain. He had a temperature of 102 F. for two days after the original nodule formed, but has had a normal temperature since then.

Laboratory Findings.—The urinalysis and the serologic test for syphilis were negative. The white blood cell count was 7,900, with 54% neutrophiles, 44% lymphocytes, and 2% eosinophiles. The hemoglobin was 13 gm., with 5,200,000 red blood cells. The complement fixation titer for Coccidioides was 1:32 before therapy and after it was discontinued. The coccidioidin test was positive before initiation of therapy and did not change after therapy. The skin tests were negative for Histoplasma and Blastomyces. The spinal fluid was normal. The biopsy from the nodule on the chest was positive for Coccidioides. The guinea pig inoculation was also positive for Coccidioides. The blood urea nitrogen was 16 mg. per 100 cc., and the fasting blood sugar was 93 mg. per 100 cc. The liver function tests (serum bilirubin, thymol turbidity, direct van den Bergh, and cephalin flocculation) were all normal. The 17-ketosteroids were 19 mg. per 24 hours. The chest x-ray and complete bony skeleton survey were normal. There was an aspermia six weeks after therapy was discontinued. He had no sperm counts before therapy.

Hospital Course.—The patient was given 35 mg. of diethylstilbestrol orally for 60 days, with no change in the lesions. He was then given 100 mg. of diethylstilbestrol intramuscularly for 100 days, with no change in the lesions, which continued to drain sporadically.

Fig. 3.—Coccidioidal granuloma which is draining. (Armed Forces Institute of Pathology #53-20314-B Ainst 13464-B.)

COMMENT

In spite of the fact that there have been several reports on the in vitro fungistatic activity of diethylstilbestrol on C. immitis, there have been no reports of its use in the treatment of coccidioidomycosis.

The dose of diethylstilbestrol to obtain its estrogenic action is usually 5 to 10 mg. orally per day. Since we wished to obtain not only its hormonal effect but also its chemical action on fungistasis, the patients received 100 mg. per day intramuscularly over a period of 63 to 100 days.

Large doses of estrogens (50 to 100 mg. per day) in males will produce atrophy of the testes, with decreased spermatogenesis, gynecomastia, and decreased libido. Frequently small doses (5 to 10 mg. per day) will produce gynecomastia alone when administered over a period of two to three weeks. There have not been many case reports showing the effects of large doses of estrogens administered to young males. In our patients, gynecomastia with minimal tenderness on palpation, appeared in two weeks and progressed very little during the remaining period of therapy. In one patient, the gynecomastia decreased but was still present 16 weeks after therapy.

The decreased libido occurred in three weeks and progressed minimally over the remaining period of therapy but returned to nearly normal levels three to four weeks after discontinuation of therapy. Unfortunately, sperm counts were not done before therapy was initiated, but 12 weeks after cessation of therapy the sperm production was either greatly decreased or totally absent. One cannot predict whether the testes will cease producing sperm, but it is known that administration of large doses of diethylstilbestrol to males will affect sperm production permanently.[3] This finding should limit the administration of large doses of diethylstilbestrol in males to rather serious diseases. There were no other symptoms from the administration of these doses, and there were no other signs, such as telangiectasis, which may appear with cirrhosis when estrogenic levels in serum may be elevated. The laboratory findings, including the 17-ketosteroids, were normal before, during, and after therapy.

The lesions of coccidioidomycosis were not changed either during or after estrogenic therapy. In one case, a large subcutaneous abscess appeared during the 90th day of treatment. This abscess was evacuated and revealed purulent, tenacious, straw-colored fluid, which was positive for Coccidioides immitis.

SUMMARY

Two patients with cutaneous coccidioidomycosis were treated with daily intramuscular injections of diethylstilbestrol for 63 to 100 days, with no effect on the lesions. They developed gynecomastia and decreased libido, which was no severer than with more conventional doses. The markedly decreased sperm counts following therapy should limit the administration of large doses of diethylstilbestrol to serious diseases.

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OPHIASIS

Report of Two Cases

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Ophiasis is a form of alopecia areata. It is relatively rare, but deserves special mention because of its different morphology, localization, and prognosis.

Alopecia areata is one of the earliest known dermatologic entities, having been described in the Papyrus Ebers, which dates back to 1500-2500 B.C.[1] The special ophiasitic form was recognized by Celsus,[2] and is so named because of the symmetric bands of alopecia above the ears on the lateral aspects of the scalp, resembling a serpent.

It usually begins near the midline of the occiput as an oval plaque of alopecia having the larger axis vertically. Later, secondary plaques form behind the ears and enlarge anterially above and in front of the ears and posterially to fuse with the original plaque.[2] The spread of the alopecia is confined to a horizontal, symmetric band which rarely exceeds more than 1 to 3 in. (2.5 to 8 cm.) in breadth and rarely involves the frontal scalp* or the entire scalp.† No inflammation is present; hair follicles are seldom visible in the bald areas, and hairs cannot be plucked from the periphery of the lesion.[4] Alopecia areata in infants usually occurs as

* References 2 and 3.

† References 4 and 5.

ophiasis,[2] which has been considered commoner in prepubertal children but also occurs in adults.‡ It may heal, and when it does the average duration is reported to be 15 or 20 months[2]; but, in general, the prognosis is serious and relapse is to be expected if the hair regrows, final restoration being rare.§

REPORT OF CASES

CASE 1.—Exceptionally bright 11-year-old boy (Fig. 1) had an irresponsible mother and an alcoholic father who beat him frequently. This boy was admitted to a mental institution after several suicidal attempts. The nature and extent of his alopecia remained unchanged during a three-year observation period. At no time could hair be plucked from the periphery of a lesion.

Figure 1.

Figure 2.

Cutaneous biopsy from an alopecic area revealed normal skin except for the absence of hair follicles—as determined by microscopic examination of sections stained with hematoxylin and eosin and the Van Gieson stain, and the polariscopic examination of an unstained deparaffinized section 30 μ thick.

CASE 2.—A 27-year-old married white woman had endured the alopecia shown (Fig. 2) for at least 10 years. The appearance of the opposite side of the scalp was identical. The alopecia was successfully concealed by her coiffure. She did not permit biopsy and did not return for further examination.

‡ References 3 and 4.

§ References 4 and 6.

CONCLUSIONS

Ophiasis should be distinguished from other forms of alopecia areata because of (1) the characteristic symmetric bands of alopecia along the lateral margins of the scalp; (2) the absence of hair follicles within the lesion, and the absence of extractable hairs at the margins of the lesion; (3) the poor prognosis. Dermatologists usually promise regrowth of hair to patients with alopecia areata, but caution is advised in ophiasis.

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ADVANCE IN MANAGEMENT OF ORIENTAL LEISHMANIASIS

Preliminary Report

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Streptomycin has not been reported previously for the treatment of Oriental leishmaniasis, although several other antibiotic drugs have been employed.* This report deals only with the treatment of Oriental leishmaniasis and does not include the American type, although treatment in allied protozoal infections is recommended.

Dihydrostreptomycin was used in the treatment of 133 cases of Mediterranean Oriental leishmaniasis of all varieties. The drug may be injected locally into the lesions or given parenterally or by both methods, and is equally effective by either technique. Local injections into single lesions is inexpensive and usually not more than three injections are needed in such cases. According to the size of the lesion, 0.25 to 0.5 gm. in 1 to 4 cc. of distilled water or saline may be injected locally. If the site is unfavorable for local injections or in large lesions of long standing and in small children, the systemic treatment is recommended (Figs. 1*A* and 1*B*). The total systemic dose varies, although an average dose of 0.2 gm. per kilogram of body weight is advisable for most patients. Adults may require a total of 5 to 15 gm. for healing, although it is rare that more than a total of 25 gm. is needed (Figs. 2*A* and 2*B*). Continuous single daily doses of 0.5 to 1.0 gm. is advisable, and not less than 0.5 gm. daily for children.

The effect of dihydrostreptomycin treatment in the various clinical manifestations of leishmaniasis† is usually determined by the histopathologic features of the lesion. Early cases without marked epithelioid cell proliferation and with demonstrable organisms respond best to treatment. The drug prevents lesions with a lupoid trend from resulting in a more pronounced proliferative stage. Early lesions, which comprised 40 to 50% of our cases, showed quick disappearance of Leishmania tropica organisms following treatment. Dramatic results were obtained in patients with the ulcerative crater lesions (Figs. 3*A* and 3*B*). Likewise in those

* References 1 and 2.

† References 3 and 4.

Fig. 1.—*A*, multiple tuberous, ulcerous, crustaceous lesions of leishmaniasis. Leishmania tropica found. Duration four months. (Note flies as presumed vectors.) *B*, one week after dihydrostreptomycin, total 3.5 gm.

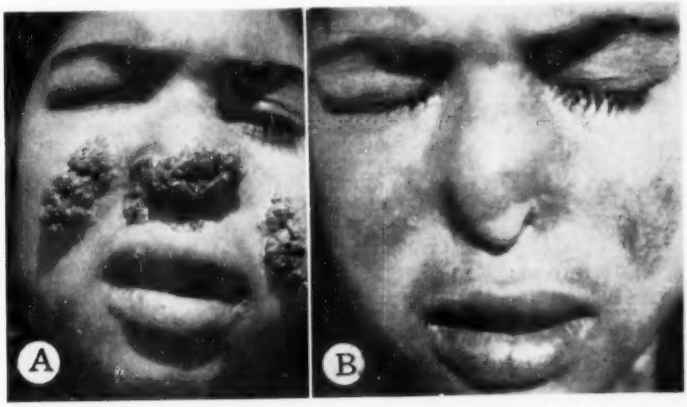

Fig. 2.—*A*, granulomatous, crustaceous (yaws-like) leishmaniasis. Duration six years. L. tropica found intracellularly. *B*, after dihydrostreptomycin, 30 gm. total dosage; healed with smooth scars, and mutilation of soft parts.

Fig. 3.—*A*, ulcerous leishmaniasis, resembling ulcerative carcinoma. Leishmania tropica found in masses. Duration five months. *B*, picture taken six days after dihydrostreptomycin, 5 gm.

with erythematous lesions with hyperkeratotic follicular plugging, verrucous granulomas of the fingers and granulomas of the lips also responded well to therapy (Fig. 4). A follicular lichenoid leishmanid was noted in one patient after several injections of dihydrostreptomycin (Fig. 5). This suggests the possibility of a leishmanicidal effect of therapy, since similar observations have been noted in the effective treatment of cutaneous tuberculosis.

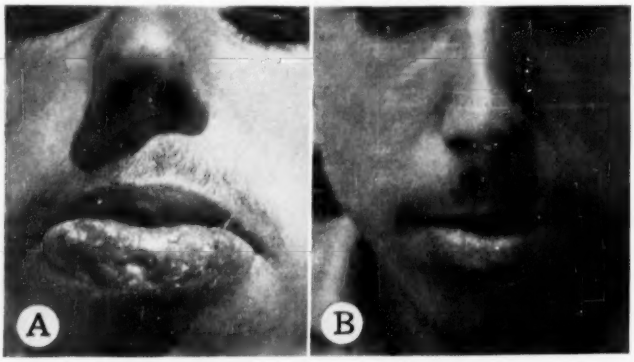

Fig. 4.—*A*, cheilitic, granulomatous leishmaniasis of lower lip. Leishmania tropica found. Duration one and a half years. Previously penicillin and antimony course given without response. *B*, picture taken three months after dihydrostreptomycin, total 28 gm.

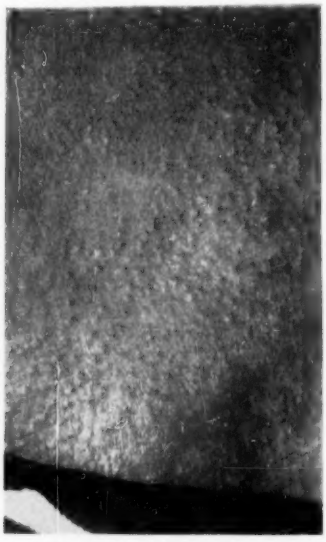

Fig. 5.—Follicular lichenoid leishmanid, sternal region. Arisen in lupus erythematosus-like leishmaniasis of face of 10 years' duration, after dihydrostreptomycin, 5 gm.

Lupoid leishmaniasis is frequently seen in Iraq, but has only been infrequently reported in the literature.‡ It responds poorly to streptomycin therapy, especially in the late stages in the

‡ References 5 to 8.

presence of an epithelioid cell histologic structure. However, even these lesions seem to respond better than with former medications. The use of vitamin D_2 and electrocoagulation may be necessary in treating this form of leishmaniasis.

SUMMARY

Dihydrostreptomycin was of value in healing all varieties of 133 cases of Oriental cutaneous leishmaniasis. Early lesions responded promptly to either the local infiltration or systemic treatment with dihydrostreptomycin. Treatment of early lesions may prevent a lupoid form from developing. Dihydrostreptomycin was less effective in patients in whom the Leishmania tropica organism was not demonstrated in the ulcers or in those who had a tuberculoid histological structure. Vitamin D_2, electrosurgery, and ultraviolet light are valuable adjuncts in the treatment of lupoid lesions. Dihydrostreptomycin, at present, seems to be the treatment of choice in the majority of cases of Oriental cutaneous leishmaniasis.

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GREENISH FLUORESCENCE OF SCALP HAIRS FROM QUINACRINE HYDROCHLORIDE ADMINISTRATION

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On prolonged administration quinacrine (Mepacrine; Atabrine) hydrochloride, sometimes produces greenish yellow fluorescence in the nails, skin, and mucous membranes.* Recently we observed green fluorescence of scalp hairs in a patient receiving quinacrine hydrochloride for chronic discoid lupus erythematosus.

REPORT OF A CASE

A 54-year-old Negro woman consulted us in May, 1953, because of several circumscribed areas of alopecia, in which there were erythema, scaling, infiltration, atrophy, and accentuation of follicular orifices. Treatment was instituted with quinacrine, 100 mg. three times daily. Two

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* References 1-3.

weeks later a yellow tint of her skin was noticed, and she complained of pruritus of the scalp. Wood's light examination disclosed that the proximal 2 in. (5 cm.) of all the hairs on the vertex and occiput exhibited bright green fluorescence indistinguishable from that observed in cases of tinea capitis due to the Microsporum group (Figure). Direct KOH examination of hairs and cultures of hairs were negative for fungi on three occasions. The drug was discontinued after four weeks, and two months elapsed before the green fluorescence disappeared. The lesions of lupus erythematosus regressed. Six months later the drug was reinstituted experimentally in the same dosage. In two weeks the fluorescence of hairs was again visible. Hairs on other parts of the body remote from the scalp were not affected. After the drug was stopped, the fluorescence disappeared in two months. Direct KOH examination of the fluorescent hairs and cultures were again negative on three occasions.

Florescence of hairs from quinacrine hydrochloride.

SUMMARY AND CONCLUSIONS

1. It was observed for the first time that quinacrine (Mepacrine) hydrochloride is capable of producing green fluorescence of scalp hair.

2. On visual inspection the fluorescence is indistinguishable from that seen in cases of tinea capitis due to the Microspora.

3. Quinacrine hydrochloride may produce in hair a chemical fluorescent indicator substance similar to the small molecule polypeptide responsible for fluorescence when the Microspora are present.

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TREATMENT OF DERMATITIS REPENS WITH PERUVIAN BALSAM

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AND
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This report of three cases of dermatitis repens is presented because of the rapid and striking therapeutic results obtained in each case with 10% Peruvian balsam in petrolatum after many previous attempts at therapy had failed.

The entity of dermatitis repens is rather poorly defined. Its differential diagnosis includes acrodermatitis continua of Hallopeau, pustular psoriasis, acrodermatitis pustulosa perstans of Sachs, and pustular bacterid of Andrews. The clinical, histological, and pathological features which are said to distinguish these conditions are equivocal. We have diagnosed dermatitis repens here because the cases fitted Radcliffe-Crocker's original description [1] well.

REPORT OF CASES

CASE 1.—T. W., a 53-year-old white machinist, first noted a small horny growth on the fifth digit of the left foot six months prior to admission to our clinic. In fingering the lesion, the patient had pulled off the "growth," leaving an open sore, which then slowly spread peripherally despite various local treatments. Eleven weeks later a blister developed on the medial aspect of the same foot and initiated another similarly progressive recalcitrant lesion. Still later, similar lesions also developed on both heels.

When the patient was seen by us, there was, primarily, a bright red oozing area involving the dorsal surfaces of the fourth and fifth toes and the plantar surfaces of all toes of the left foot (Fig. 1). A collarette of partially detached epithelium surrounded the lesion. Similar lesions were present on the medial aspects of both heels. On hospitalization, routine laboratory tests and physical examination, except for the skin changes, were essentially normal. Cultures from the foot lesions revealed coagulase-positive hemolytic Staphylococcus aureus. Numerous direct examinations and cultures for fungi revealed occasional Aspergillus contaminants. The trichophytin test was negative.

For the first 31 days of hospitalization, all therapeutic attempts failed. These attempts included local application of silver nitrate wet dressings, ammoniated mercury ointment, methylrosaniline chloride (gentian violet), and bacitracin solutions, and a prolonged course of oral oxytetracycline. After the 31st day, 10% Peruvian balsam in petrolatum was applied twice daily. Exudation ceased immediately, and complete healing occurred in two months (Fig. 2). At the present time, 24 months after treatment, there has been no recurrence.

CASE 2.—L. N., a 34-year-old, white plumber, when first seen gave a history of mild recurrent "athlete's foot" of 16 years' duration. He considered his presenting severe illness to have begun nine months previously as a flare-up of this "athlete's foot." Despite various local treatments elsewhere, the condition failed to improve, and about one month before he consulted us, a denuded oozing patch developed on the ball of the right foot and enlarged slowly.

When he was first seen, there was denudation of the skin of the plantar surfaces of all toes of the right foot extending to the interdigital spaces. A foul-smelling purulent discharge exuded from this reddened area, and an undermined epidermal collar surrounded the lesion. Cultures of the lesion revealed Aerobacter aerogenes on one occasion and Psuedomonas aeruginosa on another. Direct examinations and cultures for fungi were negative. Except for the lesion, physical examination and routine laboratory tests were essentially normal.

After five weeks of unsuccessful therapy with various wet dressings, bland pastes, and several antibiotic ointments, 10% Peruvian balsam in petrolatum was applied locally. Four days later exudation ceased, and after two more days epithelialization was noted. The patient recovered completely and returned to normal activity within one month.

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Dr. Stephen Rothman gave advice on the preparation of the manuscript.

Fig. 1 (Case 2).—Right foot before treatment with Peruvian balsam.

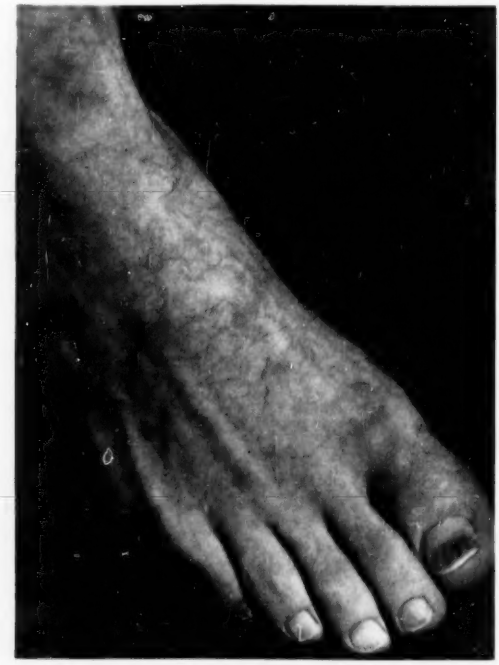

Fig. 2 (Case 2).—Right foot approximately three weeks after treatment with 10% Peruvian balsam in petrolatum.

Approximately nine months later there was recurrence of this patient's skin disorder. This episode again responded promptly and dramatically to Peruvian balsam ointment, and the patient has been symptom-free for the past eight months.

CASE 3.—W. B., a 62-year-old white salesman, complained of "weeping eczema" of the dorsa of the toes of the right foot almost constantly present for three years. The left foot had been amputated in the past for severe neuropathic joint changes complicating pernicious anemia, which was thereafter well controlled with liver extract.

Examination of the skin revealed denudation of the dorsa of the toes of the right foot, leaving a raw, acutely inflamed surface. Direct examinations and cultures for fungi were negative. General physical examination and routine laboratory tests were noncontributory.

After 17 months, despite various attempts at therapy, which were sometimes followed by temporary improvement, the lesion presented an essentially unchanged appearance. Cultures of the purulent exudate on several occasions revealed Pseudomonas aeruginosa, Streptococcus faecalis, beta hemolytic Streptococcus, Escherichia intermedium, and Paracolobactrum aerogenoides. The in vitro antibiotic sensitivities of these organisms were tested. However, treatment with the antibiotics to which most of these organisms were sensitive failed to be effective clinically. It should be mentioned, however, that the Pseudomonas aeruginosa in this case was completely resistant to all 10 of the antibiotics we had available for testing.

Effect of Peruvian Balsam on Antibiotic-Resistant Organisms

	Pseudomonas Aeruginosa	Aerobacter Aerogenes	Bacillus Proteus	Pseudomonas Aeruginosa	Pseudomonas Aeruginosa	Pseudomonas Aeruginosa	Hemolytic Staphylococcus Aureus	Hemolytic Staphylococcus Aureus	Aerobacter Aerogenes	Hemolytic Staphylococcus Aureus	Candida Albicans
Peruvian balsam 1.25%.	—	—	+	—	—	—	++	++	+	++	++
Peruvian balsam 2.5%..	—	+	+	—	—	—	+++	+++	+	+++	+++
Peruvian balsam 5.0%..	+++	+++	+++	—	+	+	+++	+++	++	+++	+++
Peruvian balsam 10.0%.	+++	+++	+++	++	+++	++	+++	+++	+++	+++	0

Key: +++, sensitive; ++, moderately sensitive; +, slightly sensitive; —, resistant; 0, not tested.

Finally, 10% Peruvian balsam in petrolatum was applied locally twice daily. Complete healing of the lesion occurred within two weeks. Subsequently there has been no recurrence after nine months of normal activity.

We studied the antibacterial effect of Peruvian balsam on antibiotic-resistant organisms by using various concentrations of the agent emulsified in brain veal agar culture medium. As can be seen from the Table, the results are in accord with those of Bräutigam and Novak,[2] who found that a relatively high concentration of the agent was necessary for complete inhibition of bacterial growth. Still, the bacteriostatic effect of Peruvian balsam in practicable concentrations on some antibiotic-resistant strains should be noted.

COMMENT

In all of our cases the disease tended to spread by denudation of the lesions peripherally without the appearance at the active border of closed vesicles or bullae. The exudate from the lesions was characteristically profuse and foul smelling. Earlier authors * believed that dermatitis repens was always caused by strains of hemolytic Staphylococcus aureus of distinctive pathogenicity. Lately Post and Hopper [5] have noted the culture of pure strains of Pseudomonas from such lesions. In their two cases, antibiotics had been used prior to culturing, and perhaps other organisms had been present originally. Experience since the advent of the antibiotics seems to indicate that the flora in dermatitis repens is not distinctive, and thus the role of bacteria in this disease remains to be clarified.

* References 3 and 4.

The medicinal properties of Peruvian balsam were noted by the Spanish conquistadors who discovered its use among the South American Indians. Monardus of Seville[6] wrote in 1568 of its value in preventing the appearance of pus and in promoting the healing of indolent ulcers. In the 19th and early 20th centuries, Peruvian balsam was used in Europe in combination with silver nitrate as the so-called Mikulicz ointment[7] (1% silver nitrate, 10% Peruvian balsam in petrolatum). It was claimed to be of value in torpid ulcerations by promoting granulation and epithelialization.

According to the United States Dispensatory,[8] Peruvian balsam is a complex of resins and volatile oils, the latter reputedly being responsible for its therapeutic value. The most important components are benzyl cinnamate and cinnamyl cinnamate and benzyl benzoate. In addition there are small quantities of benzyl alcohol and an agent called "peruviol." It is to the latter that the drug owes its characteristic odor.

SUMMARY

Three cases of dermatitis repens as described by Crocker are presented because of their striking response to treatment with 10% Peruvian balsam in petrolatum after prolonged antibiotic therapy had failed. The history and pharmacology of Peruvian balsam are briefly reviewed.

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Society Transactions

BRONX DERMATOLOGICAL SOCIETY

Nathan Sobel, M.D., ***President***

Henry Silver, M.D., ***Secretary***

March 18, 1954

Necrobiosis Lipoidica. Presented by Dr. Frances Pascher and Dr. Sidney C. Clyman (by invitation).

This is a 52-year-old Norwegian woman with lesions on the legs and thighs since the age of 32. New lesions have appeared on the upper extremities since the onset. Diabetes was not present in the past, nor has it appeared in this interval of time.

During a course of quinacrine (Atabrine) therapy, some of the lesions have improved. The application of local 2.5% hydrocortisone acetate ointment for three weeks produced no clinical change. Cortisone acetate was started on May 18, 1953, 100 mg. given three times daily, 75 mg. twice, 50 mg. four times a day; then 25 mg. daily until July 30, 1953. Thyroid, 1 grain, was given daily at the same time. No change in the lesions occurred. The over-all clinical appearance is in general very little changed.

Glucose Tolerance Tests

	Fasting	½ Hr.	1 Hr.	2 Hr.
Oct., 1952	65	85	70	65
April, 1953	70	85	75	70
Aug., 1953 (On cortisone 6 wk.)	70	105	85	85

The basal metabolic rate in May, 1953, was —12. Cholesterol in May, 1953, was 225 mg.

The patient received a tablet of quinacrine, 1.5 grain b. i. d., from Dec. 6, 1952, to Feb. 14, 1953, and towards the end of the treatment period was on three tablets daily.

Histologic examination: "Throughout the cutis are areas of degeneration. In the latter is seen parenchymatous edema of the collagen with degeneration. In these areas are aggregations of cells composed of small round cells, wandering connective tissue cells, multinucleated cells, and, in some areas, plasma cells. In the cells of the overlying epidermis the nuclei appear to be vesicular. There are no other noteworthy pathologic features. Fat is deposited in all degenerated areas of the section in the Sudan III stain.

DISCUSSION

Dr. Frances Pascher: This patient was presented by Dr. Biberstein in 1952 and is presented again tonight because of additional laboratory data. In the course of a search of the literature on necrobiosis lipoidica Dr. Clyman found that this patient was originally presented in 1938. At that time the diagnosis favored was necrobiosis or granuloma annulare. The diagnosis of necrobiosis lipoidica, despite some unusual clinical features, was accepted by the members of this Society when she was presented in 1952. The unusual laboratory feature is the abnormal glucose tolerance curve in the direction of hypoglycemia rather than hyperglycemia; this patient has increased tolerance to sugar as compared to the normal figure.

Dr. Sidney C. Clyman: In 1929 Dr. Oppenheim first described the condition known as necrobiosis lipoidica, and diabetes mellitus was considered to be a vital part of the disease. However, in the ensuing years, cases appeared in the literature in which diabetes was not present. In 1940, in an extensive review of 87 cases of necrobiosis lipoidica, 10% were found not to have diabetes. Now recorded cases show only 40% to be diabetic. This is of particular interest to us. The case presented tonight, showing a low flat glucose tolerance curve, does not fit in with the accepted patterns. If this were the first case to show this type of reaction,

we might say it was a coincidence, but a review of the literature shows many cases presented throughout the country with the type of pattern presented tonight. However, there has as yet not been any extensive research brought out in the literature. Following the ingestion of glucose, this patient presented a lack of the rise originally expected. This is not typical of hypoglycemia because the levels do not drop low enough. True hypoglycemia may be seen in hypertrophy or tumor of the hyaline glands of the pancreas, in insufficient function of the anterior lobe of the pituitary gland, in hypothyroidism or adrenocortical insufficiency. So-called hypoglycemic patterns are also found in liver diseases, following faulty absorption of glucose from the intestinal tract, and in functional nervous disorders. Here we have a unique dermatologic condition, with both extremes of glucose metabolism. This case is presented tonight to stimulate further biochemical investigation and to reemphasize that not only may there be a normal glucose tolerance curve in necrobiosis, but also a tendency to a hypoglycemia curve.

DR. ALEXANDER A. FISHER: There are apparently no statistics on the incidence of necrobiosis lipoidica on the upper extremity as compared with the lower. The lesions on the arms and forearms are unusual. May one expect that in the future these soft, unusual lesions will become infiltrated and take on the appearance of typical necrobiosis? Or will the lesions of the upper extremity always differ from those on the lower extremity, because of differences in anatomy and circulation in the two areas?

DR. FRANCES PASCHER: Lesions on the upper extremity are exceptions rather than the rule. They have been noted before, however. Another interesting feature of this case is that the lesions have shown little or no tendency to ulcerate. Ulceration is not a *sine qua non* as exemplified by an unquestionable case of necrobiosis shown here this evening. The presence or absence of ulceration may be a matter of intensity rather than quality of the necrobiotic process.

Xanthoma Tuberosum Multiplex. Presented by DR. JOHN GARB.

DISCUSSION

DR. FRANZ HERRMANN: I believe that we are dealing here with an "eruptive" form of xanthoma (Thannhauser). The history and lesions are suggestive of the idiopathic hyperlipemic, rather than of the familial hypercholesteremic type. The nodules are relatively small, very numerous, rather evenly disseminated, and the tendons are apparently not invaded. The condition appeared relatively late in life. The blood serum is probably creamy, because of an excessive total of lipids. If this is confirmed, low-fat diet should be beneficial.

DR. JOHN GARB: Blood for lipid partition studies has already been taken, but only the cholesterol level, 435 mg. per 100 cc., has thus far been reported.

The patient presents typical tuberous xanthomatous lesions on the extensor surfaces of the knees, elbows, ankles, and other areas. I agree with Dr. Herrmann in so far that there may be an additional element of eruptive hyperlipemic xanthomatosis on the trunk and extremities because of the patient's habit of eating fats, sugar, and starchy foods.

The immediate members of his family are unavailable for testing for possible hypercholesteremia.

At the Rockefeller Institute, experimental work is now being performed with a high-fat and low-cholesterol diet. In the March 13, 1954, issue of the *Journal of the American Medical Association*, page 935, there is a report of the use by Dr. Cottet and his associates, of Paris, of phenyl-ethyl-acetic acid, a derivative of choline, with very good results.

Pemphigus Vulgaris Complicated by Diabetes, Apparently Cured with Corticotropin (ACTH) and Cortisone. Presented by DR. DAVID BLOOM.

L. F., a woman aged 54, was presented at this Society on April 16, 1953, with the diagnosis of "pemphigus vulgaris, complicated by diabetes, apparently cured with corticotropin (ACTH) and cortisone."

She was seen for the first time on Aug. 13, 1951, at the Skin and Cancer Unit, with an eruption which was diagnosed as pemphigus vulgaris and which involved both the skin and oral mucosa. She was under observation at the Clinic during four months, at which time the eruption became worse, and she was admitted to Sydenham Hospital on Dec. 13, 1951, where she was treated with corticotropin and cortisone. She was discharged on Feb. 13, 1952. After

her discharge from the hospital the patient continued to take cortisone and was treated at the same time at the Diabetic Clinic with diet and insulin. The dosage of cortisone was gradually and cautiously reduced from 400 mg., and finally discontinued in October, 1952. Since then the patient has developed occasional small bullae which dried up spontaneously. When seen several months ago she was in good health, and her diabetes was controlled by diet.

Actinomycosis and Squamous Cell Epithelioma. Presented by DR. DAVID BLOOM.

Favus. Presented by DR. ANDREW G. FRANKS and DR. EMANUEL MUSKATBLIT.

Adiposonecrosis Neonatorum. Presented by DR. CHARLES F. SIMS and DR. IRVING D. EHRENFELD.

Pemphigus Vulgaris. Presented by DR. MAURICE UMANSKY.

Necrobiosis Lipoidica. Presented by DR. FRANCES PASCHER.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. FRANCES PASCHER.

Pigmented Nevus of Shaft of Penis. Presented by DR. JOSEPH L. MORSE.

Case for Diagnosis. (Factitial Ulcer? Granuloma? Necrobiosis Lipoidica? Tuberculosis Cutis?). Presented by DR. ABRAHAM J. ORFUSS.

Prickle Cell Epithelioma. Presented by DR. ALEXANDER A. FISHER. (Original diagnosis, presented Oct. 18, 1953, "Persistent Superficial Ulceration of the Nose.")

Fibrosarcoma. Presented by DR. NATHAN SOBEL. (Original diagnosis Neurofibroma?).

Lymphocytic Infiltrations of the Face. Presented by DR. MAX WOLF.

Larva Migrans. Presented by DR. IRVING D. EHRENFELD.

Case for Diagnosis. (Parapsoriasis Guttata?). Presented by DR. IRWIN I. LUBOWE.

Case for Diagnosis. (Light Sensitivity Dermatosis? Papular Urticaria? Atopic Dermatitis?). Presented by DR. ALEXANDER A. FISHER.

Cellular Nevus with Junctional Elements. Presented by DR. MAX WOLF.

Granuloma Annulare. Presented for suggestions and therapy by DR. ALEXANDER A. FISHER.

Folliculitis Decalvans (Quinquaud's Disease). Presented by DR. ELLEN REINER.

Nathan Sobel, M.D., *President*

Henry Silver, M.D., *Secretary*

April 15, 1954

Vitiligo Treated by Local Applications of 8-Methoxypsoralen. Presented by DR. NORMAN B. KANOF.

C. C., a white man aged 36, had areas of depigmentation of the skin on various parts of the body for 18 years. The first areas to appear were over the elbows and were followed in rapid succession by other areas on the neck, trunk, and extremities. One sister (there are five siblings) also has vitiligo.

The patient was treated unsuccessfully about 10 years ago with bergamot oil, and there has been little, if any, change in the condition during all these years.

Applications of 1% 8-methoxypsoralen in alcohol and acetone followed by exposure to ultraviolet light and natural sunlight were begun on April 25, 1953, and continued at weekly intervals until Jan. 6, 1954. On several occasions reactions consisting of erythema and vesiculation followed the treatments but quickly responded to soothing wet dressings. Treatment was at first limited to the elbows but later included other areas.

New pigment was first observed in the elbow lesions on June 20, 1953, two months after starting treatment. Rapid filling of these areas occurred. Little progress was seen in the other areas until the patient went to Florida in January, 1954, and applied the medicine before sun exposure. New islets of pigment appeared in the lesions near the right ankle, on the left thigh, and near the knees. There has been no change in the lesion on the anterior surface of the neck.

Vitiligo Treated by Local Applications of 8-Methoxypsoralen. Presented by DR. NORMAN B. KANOF.

H. C., a Negro boy aged 15, has had areas of depigmented skin on his face, trunk, and extremities for five years.

He received no treatment prior to May 11, 1953. At that time applications of 1% 8-methoxypsoralen in alcohol and acetone were begun at weekly intervals. The applications were followed by exposure to sunlight, starting with five minutes and gradually increasing the time of exposure as treatment progressed. Treatments were given regularly for three months and irregularly from September, 1953, to the present time.

Overexposure of treated lesions on the face was a common occurrence, and erythema and crusting frequently resulted.

New pigment formation was noted in the face lesions on June 8, 1953, one month after treatment was started, and has remained in a spotty pattern since then. Spotty new pigment has also been noted in the area at the back of the neck and on the forearms.

DISCUSSION

DR. ABRAHAM J. ORFUSS: I should like to know if any repigmentation occurred in the control sites at the time the other sites were treated. Was there any spontaneous repigmentation on the nontreated areas at all?

DR. VICTOR H. WITTEN: In general, how long was it before repigmentation took place? Were there control areas which received just ultraviolet light or were the control sites left untreated?

DR. DAVID B. BALLIN: Has any attempt been made to enhance the effect by the use of wetting agents incorporated into this medicament?

DR. IRVING D. EHRENFELD: It is interesting that the agent acts as a light absorbant agent. A good method of investigation would be to apply Meladinin (a preparation containing ammoidin and ammidin), and allow a period for absorption, and then remove it to allow the light to act on the skin. It might account for the irregularity of the result.

DR. HENRY SILVER: I for one enjoyed Dr. Kanof's factual presentation and modest evaluation of the results obtained with 8-methoxypsoralen. It is a welcome relief from the over-optimistic and full-of-wishful-thinking reports one usually encounters whenever a new drug is introduced.

I am concerned with the blistering effect. Is it considered optimum? Is there a relationship between the degree of the photosensitizing reaction and repigmentation?

DR. RUDOLF L. BAER: I also want to congratulate Dr. Kanof on his clear, concise, and conservative presentation. It is of interest that there is some difference in the technique used by Dr. Kanof and that used by Drs. Sidi and Bourgeois-Gavardin in Paris. It appears possible that this accounts for the difference in results also. I do not remember the exact figures reported by the French investigators, but I believe that they started with 115 subjects and ended with 85 who actually continued the treatment long enough so that the results could be evaluated. Among these 85 subjects, 17 had very satisfactory clinical results and another 15 had fairly good results. The French group treated their patients practically daily, while Dr. Kanof treated his patients once a week. Furthermore, they stressed that one should apply the photosensitizing substance about one hour before the treatment is to be administered; it should then be removed from the skin surface before the light treatment is given. Otherwise, the material still on the skin surface acts as a light filter and in that way actually interferes with the effect that one is trying to achieve. I should also like to stress that these French authors discussed the question of photoallergic reactions to Meladinin in detail, with some interesting findings, which Dr. Kanof may want to mention in this discussion.

DR. FRANK E. CROSS: Dr. Kanof mentioned how long he treats these patients before he decides he cannot go any further. In the original work the Egyptians took this drug by mouth. What is the situation at present on this point?

DR. GEORGE KLEIN: I should like to know if the pigment is stationary? Does it disappear again?

DR. MAX WOLF: How does one explain a brownish pigmentation in the form of sharply defined bands on the abdomen of a patient in an area which was never painted with Meladinin, or afterwards exposed to ultraviolet radiation or to the sun? The vitiliginous parts of the hands, axillae, and inner thighs responded to the combined local and oral treatment.

DR. MORRIS LEIDER: It is a pity that the well-presented report of Dr. Kanof could not have been an account of a great success. The simple truth is that the treatment of vitiligo with 8-methoxypsoralen cannot be rated a good treatment. My own experience, like that of Dr. Kanof and others in this area, is that repigmentation by this means is irregular, varying from nothing to a fair amount but rarely complete. Moreover, whatever the effect, it takes a long time occurring and requires expensive, time-consuming adjuvant treatment with ultraviolet light.

Exposure to sunlight, it would seem to me, is contraindicated because of the severity of blistering. The hopeful thing about the situation is that melanogenesis apparently can be stimulated, even if to an uncertain and unpredictable amount by a known agent. From this beginning perhaps more effective agents may be discovered or developed.

DR. NORMAN B. KANOF: I wish to thank the discussers for their interesting comments and questions.

We used 1% of 8-methoxypsoralen dissolved in an acetone, alcohol, propylene glycol, and water "lotion," which was supplied to us by the Paul B. Elder Company, of Bryan, Ohio. The same strength solution was used in all age groups. We did not use higher concentrations or penetration-effecting vehicles, but regulated the intensity of the reaction by controlling the irradiation time following application of the drug. For technical reasons, treatments were given once a week. The results might be improved if they were to be given at shorter intervals.

New pigment formation did not occur in any "control areas" which received irradiation alone, or in any "control areas" painted with 8-methoxypsoralen without subsequent irradiation. New pigment appeared in "treated" (drug application with subsequent irradiation) areas as soon as four weeks after the onset of therapy in some instances, but in some patients it did not appear until six months of therapy had elapsed. Occasionally pigment that appeared during the course of treatment faded despite continued therapy, but in most instances, the newly formed pigment persisted as long as the patients remained under observation.

Irritation of some degree from the treatment occurred in over 40% of patients treated by our method. No instances of true "photoallergy" occurred in our series, and treatment could be continued in every case.

There appeared to be no direct correlation between melanogenesis and inflammatory response to the treatment. Pigment failed to appear in many patients who suffered severe irritation, though some degree of dermatitis did precede a recurrence of pigment in most cases.

Keratosis of the Hands. Presented by DR. IRWIN I. LUBOWE.

Metastatic Nodular Lesions of the Scalp, Ten Years after Bilateral Mastectomy for Carcinoma. Presented by DR. ALEXANDER A. FISHER.

Case for Diagnosis. (Atypical Lichen Planus? Kaposi's Sarcoma?). Presented by DR. ABRAHAM J. ORFUSS.

Recurrent Ulcers of the Mouth (Aphthous). Presented by DR. DAVID B. BALLIN.

Case for Diagnosis. (Erythema Nodosum?). Presented by DR. IRWIN I. LUBOWE.

Case for Diagnosis. (Factitial Ulcer? Nodular Vasculitis?). Presented by DR. DAVID B. BALLIN.

CHICAGO DERMATOLOGICAL SOCIETY

Julius E. Ginsberg, M.D., *President*

Irene Neuhauser, M.D., *Secretary*

May 26, 1954

Carotinemia. Presented by DR. S. M. BLUEFARB and DR. HAROLD H. RODIN, and (by invitation) DR. LEONARD HOIT.

The patient, a 32-year-old white woman, was admitted to the Cook County Hospital for uncontrolled diabetes. She has been a known diabetic since 1943. In 1939 and 1940, she lost the sight of both eyes from "cataracts." She has had three previous admissions for uncontrolled diabetes. As part of her diet, she has been eating at least one-half cup of chopped carrots daily.

Her past history is otherwise negative, and the family history is noncontributory.

On physical examination blood pressure was 158 systolic and 100 diastolic. There were diffuse orange-yellow discolored areas of the skin which were most marked on palms and soles.

Laboratory Findings: The urine was normal. Blood examination showed 90% hemoglobin and 5,800 white cells. Blood chemistry showed N.P.N. 28 mg., fasting blood sugar 234 mg., total protein 7.5 gm., and serum bilirubin 3.8 mg. per 100 cc.; icterus index 7, cephalin flocculation index 0, and thymol turbidity 3.4. Kahn reaction was negative.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati: We have learned just recently that hypothyroid children are unable to convert carotene into vitamin A. This is proved by high blood carotene levels and

low blood vitamin A levels. At the present time, we are studying an "acquired" hypothyroidism in a child in whom the blood carotene levels are over 170. Pediatricians are well aware that moniliasis may be found in hypoparathyroidism as well as in hypothyroidism.

DR. S. M. BLUEFARB: We thought it was somewhat unusual to have carotinemia not only on the palms and soles but on the face as well. This patient also has yellowing of the eyes, presumably a diagnostic point between jaundice and carotinemia. Dr. Sickley states that she had an eye injury with increased keratinization. Since carotene is deposited in the keratin layers of the skin, this may account for the presence of carotene in the eyes.

Sarcoid-like Silica Granuloma. Presented by DR. H. M. BULEY and DR. M. H. KULWIN, Champaign, Ill.

M. S., a married white woman, born in Germany 30 years ago, presents what appears to be light purplish-red keloid-like scars over the right patella, as well as a single linear lesion about 1 cm. in length on the extensor surface of the left elbow. The patient also has a normal-appearing, nonelevated and nonkeloidal scar on her right elbow and an abdominal regular scar from a recent cesarean section.

History.—Approximately 20 years ago, patient fell and abraded her right knee cap. She does not remember an injury to her left elbow. Subsequent normal, nonsignificant healing occurred, with no residual deformity of the skin except for a faint appearance of whitish, linear, nonelevated, asymptomatic scars. Two months ago, patient noticed that this old scar on her knee as well as a small linear lesion on her left elbow became livid and raised until it assumed its present appearance.

The scar at her right elbow is the result of an injury which occurred in 1947.

Laboratory Findings.—Urine was normal, as was the blood cell count. Kahn reaction was negative. Basal metabolism rate was —9%. Blood cholesterol 274 mg. per 100 cc. The glucose tolerance test gave the following result:

	Blood Sugar	Urine
Fasting	115 mg. per 100 cc.	Negative
1 hr.	158 mg. per 100 cc.	1 +
2 hr.	169 mg. per 100 cc.	Negative
3 hr.	131 mg. per 100 cc.	Negative

Roentgenological examination of the chest gave normal findings.

Histology.—Biopsy showed clusters of epithelioid cells, mixed with Langhans' giant cells and lymphocytes in the subepidermal portion of the cutis. In polarized light, brightly-shining particles are visible, usually located inside the giant cells.

DISCUSSION

DR. ADOLPH ROSTENBERG, JR.: I think all will agree with the diagnosis. One might argue a little about the word arrangement used. I think they call it a sarcoid-silicon-like granuloma. As I walked over here with Dr. Michelson, we discussed the terminology. His view, which is mine, would label this as silicon granuloma with sarcoid architecture. To call it sarcoid-like may give misleading implications. A case similar to the present one was the one presented by Dr. Ginsberg a year or so ago.

These cases are very interesting and raise a number of unsolved questions: (1) Why the scarcity? (2) Why the long latency? (3) Why the resolution? If silicon is the cause, why do such lesions not develop frequently, inasmuch as we all abrade ourselves frequently, particularly as children, and silica is an ubiquitous material. Second, the latency; many of these cases apparently appear only years after the injury. I recall a case reported in the *British Journal of Dermatology* in which the latent period was 32 years. It is very difficult to understand. As to the pathogenesis, it is usually that of a foreign body reaction, yet one can have a foreign body without developing these lesions; one does not develop this type of lesion from any kind of foreign body. An ingenious theory that has been advanced is that the lesion develops because of a so-called piezo-electrical effect. Certain crystals, including some silicates, have the physical property of responding to a small stain or deformation with the generation of an electric current. Of course, even though one can show a piezo-electric effect in these cases, it would still remain to be shown that

this is capable of causing this type of lesion to come into being. The only possible basis for such a theory is the work of Gardner on the experimental production of pulmonary silicosis. He found that the crystals which gave positive results were those that showed a piezo-electrical effect. These lesions nearly always develop in areas of skin mobility. This is advanced as an argument for the piezo-electric explanation, inasmuch as the mere presence of the crystals will not cause an electrical reaction. It is necessary for them to be subjected to strain or stress.

The final point peculiar to these cases is the question of resolution. As I recall it, the lesions in Dr. Ginsburg's patient disappeared after treatment with chlortetracycline (Aureomycin).

DR. M. R. CARO: I think that cases like this should be given wide publicity. With the sandpaper treatment that is being used now for acne scars, in 10 or 15 years instead of having a single case of silica granuloma presented at a meeting there will probably be 10 or 15.

DR. HANS M. BULEY, Champaign, Ill.: The arrangement of the lesions in parallel lines was so strongly suggestive of a superficial traumatic abrasion that we at once associated the present eruption in this case with a former injury. When we found the brightly sparkling particles under the polarizing microscope, the diagnosis was, of course, established.

In regard to treatment, however, we are quite uncertain. We shall at first try chlortetracycline therapy following Dr. Webster's experience in a similar case presented before this Society not so long ago. If this should fail, injections of hydrocortisone (Hydrocortone) will be indicated. As a last resort, we have considered the removal of the foreign particles by surgical means.

We have no explanation for the appearance of the lesions so many years after the injury. This seems to be characteristic for this type of eruption. We should like to point out, however, that the patient went through a pregnancy during the past year, during the last weeks of which she developed a pre-eclamptic state which was the indication for delivery by cesarean section. She also showed an increase in the blood cholesterol level before the skin lesions appeared. Perhaps a disturbance in the enzymatic balance in the tissue caused it to react to the imbedded silica particles.

Poikiloderma Vasculare Atrophicans (Jacobi)? Presented by DR. ALLAN L. LORINCZ (by invitation) and DR. STANLEY MESIROW (by invitation).

Mrs. M. M., a 61-year-old housewife, was first seen at the University of Chicago Clinics on May 5, 1954. She stated that about five years previously, itching developed in both inguinal areas. Shortly afterward, small red spots appeared in the itching areas, some of which later became confluent. The involved areas became scaly and dry. Approximately one and a half years ago, similar itching and lesions developed on both breasts. At the present time itching is very mild. Previous treatment has consisted of ultraviolet irradiation and local applications of various sorts.

The results of general physical examination are essentially negative. The skin reveals roughly symmetrical involvement of the breasts, inguinal, and infraumbilical areas. In these areas are discrete, dry, slightly scaling patches which are stippled throughout, with telangiectases, atrophic spots, and hyperpigmentation. The changes are similar to actinodermatitis. However, she has had no x-ray therapy.

At the present time the patient is receiving 1,200,000 units of penicillin twice a week and has received 4,800,000 units of an intended course of 10,800,000 units.

Routine studies of blood and urine revealed no abnormalities. A chest x-ray examination was negative.

Biopsy: There is atrophy of the epidermis. There is a diffuse lymphocytic infiltrate in the upper corium, which is edematous and shows disruption of the collagen fibers. There are many dilated vessels, most prominent in the lower part of the involved corium. Sweat glands and follicular epithelium are atrophic.

Diagnosis is compatible with poikiloderma vasculare atrophicans.

DISCUSSION

DR. EDWARD A. OLIVER: I think this case should be called poikiloderma-like instead of poikiloderma. In 1935, I wrote a paper on mycosis fungoides with poikiloderma-like symptoms. In looking up the literature, I found numerous cases in the current literature and in the different

society proceedings labeled poikiloderma, which should have been called poikiloderma-like. Now poikiloderma is a rare disease. As I recall, we have had only two genuine cases of poikiloderma shown before this Society, many that were poikiloderma-like. Dr. Minnie Perlstein showed one and Dr. Ormsby the other. The symptoms of poikiloderma were not all here. Jacobi's case showed considerable myositis with atrophy of the shoulder muscles, edema of the eyelids, and a cutaneous eruption, which showed pigmentation, telangiectasis, and atrophy, and resembled a healed radiodermatitis. This case shows only a few of these symptoms and I prefer to call it poikiloderma-like.

DR. ALLAN L. LORINCZ (by invitation): I appreciate this fine discussion and cannot disagree with Dr. Oliver's comments. On reviewing Jacobi's original case of poikiloderma vascularis atrophicans, his description to me rather suggested what today we would call poikilodermatomyositis. I believe the case presented here without apparent associated internal disease represents quite a different entity which nevertheless is frequently called poikiloderma vascularis atrophicans.

Our only rationale for the use of penicillin in this case is the vague general resemblance between this condition and acrodermatitis chronica atrophicans which as we know in its active phase responds rather well to such treatment.

(Addendum: After administration of 7,200,000 units of depo-penicillin, remarkable involution of all lesions occurred, together with complete cessation of itching.)

DR. OLIVER: I would like to add that one of the clearest expositions of the subject of poikiloderma was written some years ago by Dr. Oppenheim. It contains a great deal of valuable information, and he discusses several types of poikiloderma.

Lymphocytic Infiltration of Skin (Reticulose Cutanée Gougerot). Presented by DR. BERNARD YAFFE.

G. H., a 38-year-old white man, first examined in April, 1953, presented discrete, elevated, papules and nodules on the forehead, cheeks, and behind the ears. These lesions were dull red, of soft consistency and angular in outline. A few of these coin-sized lesions showed a tendency to annular and circinate arrangements. There was no eivdence of follicular dilatation, plugging, carpet-tack scales, telangiectasia, or atrophy. A history of partial resolution of individual lesions without therapy was also offered.

Biopsy of a nodule revealed a narrow epidermis with flattening of the rete layer. In the corium were striking collections of small lymphocytes, gathered in sharply circumscribed groups about blood vessels. No germinal centers were demonstrable in these masses.

The onset of this eruption was six years ago and started in the fall of 1947. Since that time, there has been a rather progressive involvement, which has been characterized by remissions and exacerbations. The course of the eruption is not affected by season or sunlight. Therapy with quinacrine (Atabrine) hydrochloride has not been effective.

DISCUSSION

DR. F. J. SZYMANSKI: There is a condition in the skin which is characterized by discrete reddish-purple nodules and plaques which microscopically show a very dense lymphocytic infiltrate throughout most of the corium. The germinal centers characteristic of lymphocytoma cutis are absent. Differentiation from a lymphoblastoma microscopically is impossible. Only time will determine whether we are dealing with a local condition or with a lymphoblastoma. Lymphocytosis cutis may be a good name for such tumors. Injection of hydrocortisone solution should produce a rapid disappearance of these localized lesions, inasmuch as lymphocytes are quickly dissolved by this corticosterone.

DR. BERNARD YAFFE: This new disease entity has been introduced by Dr. Max Jessner of New York City. Several cases have been presented before the Bronx Dermatological Society and the most recent case before the section of the New York Academy in April, 1953.

These lesions simulate discoid lupus erythematosus but without secondary or destructive changes. There is no follicular plugging, telangiectasia, scarring, or atrophy. The disease is benign and self-limited, and no sunlight sensitivity is noted. Furthermore, the patients are not benefited by quinacrine or other antilupoid measures.

Microscopically, a uniform collection of small lymphocytes, massing about blood vessels and extending throughout the corium and down to the hypoderma, is noted.

This is a most unique case, and more cases will have to be observed and studied. It is my impression that we are encountering a benign type or "forme fruste" discoid lupus erythematosus without secondary or destructive changes.

Bowen's Disease and Multiple Senile Keratoses. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. LEONARD HOIT.

Exfoliative Dermatitis (Lymphoblastoma?). Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. LEONARD HOIT.

Blastomycosis, Disseminated. Presented by DR. THEODORE CORNBLEET and DR. SIDNEY BARSKY and (by invitation) DR. LEONARD HOIT.

Dermatitis Factitia—Neurotic Excoriations. Presented by DR. THEODORE CORNBLEET, DR. SIDNEY BARSKY, and (by invitation) DR. HAROLD MARKS.

Acrodermatitis Chronica Atrophicans. Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. LEONARD HOIT.

Dento-Alveolar Sinus. Presented by DR. SAMUEL M. BLUEFARB and HAROLD H. RODIN, and (by invitation) DR. HAROLD MARKS.

Case for Diagnosis—Lymphoma? Presented by DR. DAVID V. OMENS and (by invitation) DR. HAROLD OMENS and DR. H. K. MITCHELL.

Case for Diagnosis (Lymphedema Praecox?). Presented by DR. THEODORE CORNBLEET and DR. SIDNEY BARSKY and (by invitation) DR. HAROLD MARKS.

Systematized Nevus. Presented by DR SAMUEL M. BLUEFARB and DR. HAROLD H. RODIN and (by invitation) DR. HAROLD MARKS.

Lichen Striatus. Presented by DR. SAMUEL M. BLUEFARB and DR. HAROLD H. RODIN and (by invitation) DR. H. K. MITCHELL.

Rosacea-Like Tuberculid (?). Presented by DR. J. W. DIDCOCT, Urbana, Ill.

Lupus Vulgaris: Successful Treatment with Isoniazid (Nydrazid). Presented by DR. H. H. RODIN, South Bend, Ind.

Epidermolysis Bullosa Simplex. Presented by DR. ALLAN L. LORINCZ (by invitation).

Case for Diagnosis. Presented by DR. MATTHEW J. BRUNNER.

Chronic Lupus Erythematosus with Subacute Dissemination. Presented by DR. ALLAN L. LORINCZ (by invitation) and DR. STANLEY MESIROW (by invitation).

Vulvar Lymphangiectasis. Presented by DR. JOHN B. HAEBERLIN JR. and (by invitation) DR. DAVID W. KERSTING.

Generalized Pigmented Purpuric Eruption. Presented (by invitation) by DR. SIDNEY J. KAPLAN, Waukegan, Ill.

LOS ANGELES DERMATOLOGICAL SOCIETY

J. Walter Wilson, M.D., President

Anker K. Jensen, M.D., Secretary

Feb. 9, 1954

Lymphocytic Infiltration of the Skin. Presented by DR. BEN A. NEWMAN and (by invitation) by DR. FRED F. FELDMAN.

H. M., a white woman aged 41, was first seen in January, 1953, because of a pruritic eruption consisting only of a few small, erythematous papules on the extensor surface of the forearms which had been present for several months. During hospitalization for a thyroidectomy, the eruption subsided spontaneously. She was seen again on Nov. 10, 1953, with an eruption on the extensor surface of both forearms, and there has been exacerbations and remissions of the eruption since she was last seen. On Nov. 20, 1953, the lesions on the elbows had involuted, but new lesions appeared on the knees. These had disappeared leaving residual, erythematous macules.

There are some scattered, discrete, reddish-brown papules of firm consistency, varying from 4 to 7 mm. in diameter, on the extensor surface of the forearms. Both knees present erythematous macules that are the result of smaller nodular lesions which she had had before.

The Wassermann reaction of the blood is negative, and complete blood count and urinalyses are normal.

The microscopic examination revealed the epidermis to be slightly hyperkeratotic. There is a superficial abscess in one area of the epidermis. The granular layer is absent at this site, and there is overlying parakeratosis. The granular area is otherwise intact. There is some flattening of the rete pegs. There is a relatively uniform round cell infiltrate, primarily focal but also disseminated, extending from the papillary layer of the corium to the deep cutis. The infiltrate is perivascular in some areas and independent of blood vessels in others; it shows no predilection for the appendages. In some locations the cells appear to be enmeshed in a

reticulum of light-staining connective tissue. The cells are primarily small, round cells but there also are some histocytes and occasional fibroblasts intermingled. The elastic fiber stain reveals an absence of elastic fibers in the areas of focal infiltrate.

DISCUSSION

DR. L. H. WINER: I cannot rule out a lymphoblastoma because of the numerous mitotic figures. These immature cells account for the rapid disappearance of the lesions clinically. On the other hand, if these sections were from lesions on the face, I could not rule out polymorphous light eruption. The dense perivascular infiltrate predominantly of lymphocytes is most suggestive of lymphoma.

DR. NELSON PAUL ANDERSON: I agree with Dr. Winer. I don't think we can take lightly anything Dr. Jessner says, but I have some reservations just the same. If he is bringing out a new entity, we should have photographs, photomicrographs and detailed case reports. He should prove to us that lymphocytic infiltration of the skin is a different condition from a polymorphous light eruption and from lupus erythematosus, and finally that these lesions are not the preliminary stages of a lymphoblastoma or a leukemia. The burden of proof is on the presenter. If it is agreed that this case belongs to his group, then this will be one of the few cases which does not involve the face. I am sure that I can show you sections very similar to those shown for this patient. When an eruption like this occurs on the face, I call it an erythematous type of lupus erythematosus. Now maybe it is a polymorphous light eruption. Dr. Jessner presents an entity labeled under a histopathologic term and says that he has been talking about it for 10 or 12 years. Perhaps this microscopic picture is the same as that described by Dr. Jessner. Can he say they are not going to develop into a lymphoblastoma? I think this was the most interesting case presented tonight. These remarks are not said in criticism but of skepticism.

DR. L. H. WINER: The section also showed an intraepidermal abscess of Pautrier. About 20% of the cases of premycotic mycosis fungoides have this condition.

Syringomyelia. Presented by DR. VICTOR D. NEWCOMER and (by invitation) by DR. EDWIN T. WRIGHT.

J. E., a married Negro aged 29, three weeks ago developed an infection involving the fingers of the right hand. He treated his hand by soaking it in hot water and blistered his fingers, explaining, "I didn't even feel the heat." The infected areas opened and drained considerably but they failed to heal.

He has always had broad, rough fingernails and large fingertips. In 1945 he fell from a truck, injuring his right shoulder, and in 1948 he injured the fingers of his right hand while playing ball. About 1950 he discovered that he was unable to tell the temperature of water with his right hand.

For the past six to eight months he has experienced intermittent pain in the back of the neck and shoulders and extending up behind the ears.

All of the terminal phalanges are bulb-shaped. The fingernails are thickened, roughened and deformed. This is more so on the right hand. There is some thickening and hyperkeratosis of the left palm. A small ulceration is present on the distal phalanges of the second and third fingers of the right hand.

There is a definite lack of sensation to pain and temperature over the right chest, supraclavicular area, and arm. Normal vibratory and light touch is preserved. The biceps and radial reflexes are absent on the right, while the right suprapatellar and patellar are hyperactive. Position sense is intact.

Blood count, serology, and urinalysis are negative. Examination of the spinal fluid showed the following: Cell count—2 white blood cells per c.c., globulin—negative, protein—49 mg., colloidal gold—negative, and serology—negative. E.E.G. was normal but electromyogram shows some evidence of anterior horn cell involvement in the upper right extremity.

Radiographs of both hands revealed slight rounding of the ungual tufts on the left. On the right there are deformities of the distal phalanges, with erosions and apparent resorption of the tufts and shafts, most marked in the second, third, and fifth digits. There was irregular calcification into the soft tissue at sites of resorption.

Radiographs of the chest and the cervical, lumbosacral, and thoracic spine and the skull series were reported as negative.

Scrapings from the feet and the left palm were positive for mycelial elements. Cultures were taken; however, there is not enough growth at this time to identify the organism.

Histamine skin test produced a normal response.

The ulcers on the right hand have healed gradually with boric acid soaks.

Neurology consultants advised no specific treatment.

DISCUSSION

DR. EDWIN T. WRIGHT: We presented this patient for two reasons: first, the condition is relatively uncommon, and second, because dermatologists occasionally see these patients first. After the diagnosis had been made on our service, we sent him to the neurological service, the latter concurring in the diagnosis. The disease is not common in children, but is seen most commonly in young adults or even in middle age. It most commonly affects the upper extremities, but is occasionally seen in the lower extremities. The preservation of touch and the loss of pain and temperature sensations are well demonstrated in this patient. The nail changes occurred gradually along with the neurological symptoms. It is interesting that he does have a fungus infection involving the palm of the left hand and the feet, and we feel that it is probably Trichophyton rubrum. Treatment is usually unsatisfactory. Both x-ray therapy and surgery have been used with questionable benefit. There have been no good control studies to show whether either of these modalities of therapy are useful. The disease may reach a plateau and not change for 10 to 15 years; hence any evaluation of treatment is difficult.

DR. J. WALTER WILSON: If the organism does turn out to be T. rubrum, I would suggest investigating the fasting blood sugar levels and the glucose tolerance curve, as well as the sugar content of the skin if possible. T. rubrum prefers areas low in sugar content, according to Dr. Stephen Rothman. One case under Dr. Munger's care has diabetes, however, and also T. rubrum infection.

Case for Diagnosis: Unusual Pigmentation of Little Finger. Presented by DR. NELSON PAUL ANDERSON and (by invitation) by DR. LYON ROWE.

Parapsoriasis en Plaque. Presented by DR. CLEMENT E. COUNTER and (by invitation) by DR. H. MILTON COUNTER.

Lupus Erythematosus. Presented by DR. ANKER K. JENSEN.

Multiple Basal Cell Epitheliomas. Presented by DR. NORMAN E. LEVAN.

Case for Diagnosis: Pityriasis Rubra Pilaris? Presented by DR. NORMAN E. LEVAN.

Parapsoriasis Varioliformia. Presented by DR. JEROME K. FISHER.

Lichen Planus with Unusual Lesions on the Palms, Soles, and Nails. Presented by DR. SAMUEL AYRES JR. and by DR. SAMUEL AYRES III.

Peculiar Lichenoid Eruption ("Lichen Xerotica"). Presented by DR. SAMUEL AYRES JR. and DR. SAMUEL AYRES III.

THE NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

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Feb. 2, 1954

Thibierge-Weissenbach Syndrome? Presented by DR. O. CANIZARES and DR. H. SHATIN (by invitation).

Patient: J. A. G. Sex: Male. Race: Negro. Age: 34.

Duration: Seven years.

Location: Generalized.

Description: Most of the skin surface, particularly that of the face, neck, and chest, shows patchy hyperpigmentation, depigmentation, and scaling. The chest, neck, and shoulders show telangiectasia. Most of the skin shows tightness in a patchy fashion, with patchy deep-seated induration and tenderness, particularly on thighs. The skin of the forehead shows tightness. Cheeks show very little tightness if any, and the

movements of jaws are not restricted. Axillary folds and elbows show hard nodular subcutaneous structures. Hard material has been expressed from the right elbow. Elbows are partially flexed, and abduction of arms is greatly restricted.

History: The process started in 1947 with pigmentary changes and general complaints of weight loss, slight fever, muscle weakness, and pain.

A diagnosis of dermatomyositis was initially established on the basis of a muscle biopsy. In the following years, results of skin biopsy were reported compatible with scleroderma. Meanwhile the skin changes have become more extensive. Original changes (1947) were described as scaling of the scalp, slight edema of the forehead, slight erythema of the neck and chest, and scaling of the waist line.

Severe diabetes mellitus developed in 1952. Patient was given cortisone in 1953, with some general improvement in that he developed an increased feeling of well-being. Diabetes became much milder after cortisone therapy was instituted. In October, 1953, cellulitis of the buttocks developed and since that time the diabetes has been uncontrolled.

Laboratory Data: Sluggishness of the esophagus on fluoroscopic studies. Some pulmonary interstitial fibrosis. ECG changes indicative of myocardial fibrosis.

DISCUSSION

DR. EUGENE TRAUGOTT BERNSTEIN: I think that we are dealing here with a case of poikilodermatomyositis, described first by Petges and Cléjat ("Sclérose atrophique de la peau et myosite généralisée," *Ann. dermat. et syph.* **7**:550, 1906). It has all the attributes of this disease, including atrophy, pigmentations, telangiectasia, and infiltration. I am not familiar with the Weissenbach-Thibierge Syndrome.

DR. PAUL GROSS: I fully agree with Dr. Bernstein that this is a poikilodermatomyositis with all the features: edema of the eyelids, chronic type of onset, and calcifications in the skin, and probably in the muscles of the shoulder girdle. There are typical lesions of the knuckles and over the elbows, showing a harshness of the skin which has nothing to do with scleroderma.

Thibierge and Weissenbach described a syndrome which corresponds very much to this case presented tonight and that is why Dr. Canizares chose this designation. As you can see from the record, biopsy showed changes of myositis.

DR. MAURICE J. COSTELLO: This patient also had keratosis punctate of the palms. If you looked at the normal furrows of the palms you could see indentations from which keratotic plugs had been removed. This condition antedated the generalized eruptions.

DR. O. CANIZARES: We presented this case under the name of Thibierge-Weissenbach syndrome because it presents some of the characteristics of this syndrome and also because we thought that it might help to get a good discussion.

The Thibierge-Weissenbach syndrome is characterized by scleroderma and cutaneous calcinosis. We have been able to follow this patient for several years, and he has been subject to a very carful investigation. At different times the diagnosis of scleroderma, dermatomyositis, and poikilodermatomiositis have been made. At the Veterans Hospital we have been able to follow several patients of this type which to me represent a "borderline type" of the collagen disease group. Whether the patient presents more sclerosing in one area, and telangiectasia, pigmentation or atrophy in another, is, in my opinion of little importance, as the main factor should be the underlying cause that produces those changes. These "borderline" cases seem to suggest that the etiologic factor of these diseases is the same one, and the cutaneous manifestations change according to some unknown quality in each patient.

Idiopathic Hyperlipemia with Secondary Eruptive Xanthoma. Presented by DR. BENJAMIN J. CHESTER.

Patient: H. K., white seaman, aged 27.

Complaint: Itching eruption of buttocks.

History: Early in October, 1953, a mildly pruritic eruption developed, beginning on the dorsum of the left thigh and spreading rapidly to involve the arms and waistline of the trunk.

Description: On admission to the U. S. Public Health Service Hospital, Staten Island, New York, Oct. 19, 1953, a generalized eruption was seen over the trunk and extremities but more concentrated on the buttocks. The eruption consisted of many firm, nontender, yellowish-pink, rounded, dome-shaped papules from which no contents could be expressed. The rest of the physical examination was negative, with the exception of hyperhidrosis of the palms and soles and tinea versicolor of the trunk.

Laboratory Examination: Cholesterol and serum lipid studies were done serially and reported as follows:

Date	Total Lipids, Mg. per 100 cc.	Total Cholesterol, Mg. per 100 cc.	Cholesterol Esters
10/20/53	4,180	600	...
10/30/53	.....	501	345
11/ 4/53	3,360	...	...
11/10/53	2,904	580	390
11/21/53	1,960	...	...
11/25/53	.....	376	266
12/ 4/53	2,600	...	...
12/23/53	1,810	212	166
12/25/53	1,540	275	200
	Mother		
11/ 9/53 (Nonfasting)	1,272	272	236
11/21/53 (Fasting)	860	...	...

G. I. series was normal. X-ray of the chest, normal. CBC was within normal limits. The first serologic specimen was returned from the laboratory as too chylous to make a satisfactory serologic examination, and subsequently VDRL and Mazzini tests were negative. Fasting glucose was 100 mg. per 100 cc.; serum amylase 60 units; total protein 6.7 gm. per 100 cc., with 4.7 gm. of albumin and 2 gm. of globulin per 100 cc. The cephalin flocculation was negative. Twenty-four-hour stool specimen for total lipids showed 18.6% of fat. Glucose tolerance test showed no spilling of sugar in any specimen. Fasting glucose was 109 mg., one-half hour specimen 126 mg., one-hour specimen 100 mg., two-hour specimen 210 mg., three-hour specimen 88 mg. per 100 cc. Basal metabolism rate was reported as +64. Electrocardiogram showed a normal tracing. Biopsy was done from a lesion on the left buttock and reported as showing a "somewhat acanthotic edematous epidermis. In the underlying cutis one notes an infiltration of spindle cells as well as polygonal cellular elements, many of which are definitely vacuolated. These cells extend fairly deeply into the tissue. Diagnosis: Xanthoma."

Course and Treatment.—The patient was carefully observed during his stay in the hospital, and treatment consisted of a low-fat diet starting on Nov. 12, 1953. The diet had 1,900 calories. The patient lost 3 lb. (1.4 kg.) while on the diet in the hospital. While in the hospital the original lesions which were present upon admission faded somewhat, but new ones appeared on the flanks, calves, and elbows. The patient was seen on eye consultation, and examination of the eyegrounds did not show a lipemia retinalis. The patient was advised to follow a 1,800-calorie low-fat diet upon discharge from the hospital.

Since discharge on Dec. 1, 1953, the patient has observed his diet fairly well and has continued to lose weight. All lesions except those on the thighs and buttocks have completely disappeared. These have lost their color and are now skin-colored papules.

DISCUSSION

DR. VICTOR H. WITTEN: This is a very interesting case, particularly when one considers the very high serum lipid level with so little in the way of skin manifestations.

We recently saw a woman at the Rockefeller Institute Hospital in whom the lipid level ran as high as 9,000 mg. per 100 cc. Her serum looked almost like butter when in the test tube. It is amazing when one thinks of the body and its organs passing and caring for this abundance of fatty material with otherwise near-perfect function. The only skin lesions which this patient

presented were a few small xanthomas on the soles. In addition, she had psoriasis which apparently had no relation to the high serum lipid content as there was no change in the psoriatic lesions with variations in the serum lipid levels. One manifestation, however, accompanied and was attributed to the peaks of serum lipid content—severe abdominal pain which prompted laparotomy on several occasions. The only finding on these occasions was a chylous ascites.

DR. DAVID BLOOM: Hyperlipemia may produce xanthoma lesions on the skin but, in my experience, never as large as those in xanthoma tuberosum. The diet which this patient received would never reduce the hypercholesteremia if we were dealing with a case of xanthoma tuberosum.

DR. CARL T. NELSON: We had an opportunity to see this patient some months ago at the Vanderbilt Clinic. At that time he had very characteristic and widespread eruptive xanthomata. On a low-fat diet, the hyperlipemic xanthomatosis has responded so well that now one does not see the widespread lesions he once had. The xanthomata that are associated with hyperlipemic states of this sort are characteristically of the papular disseminate type. However, Lever (Lever, W. F.; Smith, P. A. J., and Hurley, N. A.: Idiopathic Hyperlipemic and Primary Hypercholesteremic Xanthomatosis, *J. Invest. Dermat.* **22**:33, 1954) has recently described five patients with idiopathic hyperlipemia who had xanthoma tuberosum and xanthomata of the tendon sheaths in addition to lesions of the eruptive type. Moreover, four of Lever's hyperlipemic patients had unmistakable evidence of coronary heart disease. Until now we have thought that patients with idiopathic hyperlipemia did not develop the early and severe atherosclerosis seen in cases of essential familial xanthomatosis. It may well be that we shall have to revise our thinking on this point.

DR. CHARLES WOLF: I would like to say that we have here a historical array of cases which show the effect of the ingestion of large amounts of fat. It is a primary lipemia, and I would like to say, in the case that Dr. Witten referred to, that the psoriasis was a distinct manifestation of this lipemia. It has a direct relationship. I have advocated the close relationship between the ingestion of large amounts of fat and lipid skin disturbances, particularly psoriasis. Thresholds differ individually, and this particular patient reacted favorably to treatment in which the lipids were diminished in intake. The prompt response was shown afterward by the involution of dissemination of xanthoma-like lesions accompanied by the reduction of the lipids in the blood.

DR. BENJAMIN J. CHESTER: Thannhauser classifies these cases as hyperlipemias with secondary eruptive xanthoma, and he divides them into two groups, the idiopathic and the symptomatic. The idiopathic group consists of the Buerger-Grutz type, which is familial hyperlipemia in children with hepatosplenomegaly and secondary xanthoma, and the idiopathic hyperlipemia in adults, which may be occasionally accompanied by glycosuria and hepatosplenomegaly and is probably not familial. The case presented belongs to the latter group. Symptomatic hyperlipemia with secondary eruptive xanthoma is associated with four diseases in which hyperlipemia is found, namely, severe diabetes, chronic pancreatitis, glycogen storage disease (von Gierke's disease), and lipid nephrosis. These patients are not supposed to develop xanthomatous lesions unless they have a long-standing hyperlipemia of over 1,800 mg. per 100 cc. total lipids, and that is probably the reason you don't find xanthoma in hyperlipemias of short duration.

The young man presented was on an abnormal diet. He gave a history of ingesting large quantities of milk, ice cream, and other fatty foods. As soon as he was placed on a normal diet, on entering the hospital, his total lipids began to fall. This disease is supposedly a retention hyperlipemia due to defect in the deposition of fat in the fat storage depots; i. e., faulty removal of lipids from the blood. The patient did not show lipemia retinalis. However, the examination for this was not made when the values for total blood lipids had begun to fall. It is interesting that the patient showed a B. M. R. of +64. This also was done while the patient was on a low-calorie reducing diet.

The lesions are now regressing while the patient is on a reducing diet. The lesions at first looked like inflammatory papules of the buttocks but were rather hard in consistency. After a few weeks, they developed the orange-yellow color of xanthomata. The total serum lipids are now below 1,800 mg. per 100 cc., and the lesions become more skin-colored and then disappear.

Lymphocytic Infiltrate. Presented by DR. JESSE A. TOLMACH for DR. IRVING L. MILBERG.

History: Patient, a 68-year-old white man, was first seen in May, 1950. At that time, he said that he had a spot on his nose which had started to appear early in 1949. The lesion was described in May, 1950, as a raised, erythematous, sharply defined tumor, and a pronounced diagnosis of epithelioma was made. The patient was advised to have the lesion removed and examined pathologically. The patient then went to another institution where a clinical diagnosis of basal cell epithelioma was made. The lesion was described as an erythematous, solid infiltrated nodular lesion on the dorsum of the nose about 1 in. (2.5 cm.) from the tip of the nose. A biopsy was performed and the report was "chronic inflammatory nodule." Because of the resemblance to a basal cell epithelioma clinically, the lesion was desiccated and curetted, and finally healed in July, 1950.

In March, 1953, patient noted a recurrence on the upper and lower part of the scarred area. Another biopsy performed in September, 1953, was reported as "lymphocytic infiltrate." A review of the original slide revealed a similar pathologic condition, and the diagnosis of "lymphocytic infiltrate" was made.

Physical Examination: There is a pea-sized nodule at the upper pole and a suspicious indurated area at the lower border of a scarred area about 1.5 by 1.5 cm. on the dorsum of the nose. There has been no increase in size since June, 1953.

Laboratory Data: Serology, negative; urinalysis, negative; chest plate, negative; C. B. C., normal.

DISCUSSION

DR. EUGENE T. BERNSTEIN: I think this group does not fall in the recognized category of lymphoblastoma. It resembles quite well the sarcoid condition of lupus erythematosus. As far as I can recollect, Thannhauser gave a lecture at Mount Sinai, and from that I would say it should fall into the category of lipids, as an infiltration of lymphocytes without being lymphocytoma.

DR. BEATRICE M. KESTEN: The clinical and histologic picture seems rather characteristic of lymphocytic infiltration of the skin of the face. Dr. Gross suggested erythromycin for a patient we have with a similar infiltration. While the patient was receiving this treatment, all lesions disappeared.

DR. ANTHONY CIPOLLARO: I don't know much about the vagaries of the histology of lupus erythematosus, but I understand that there is one phase in the histology of lupus erythematosus in which a collection of lymphocytes has been mistaken by some as lymphocytic infiltration. Cases which have been presented as those of lymphocytic infiltration of the skin have had the clinical features of discoid lupus erythematosus. If it is true that one of the stages of lupus erythematosus of the discoid type shows this lymphocytic infiltration, then I think we cannot consider this new entity too seriously. I believe they represent another form of discoid lupus erythematosus. Some of the pathologists who are here might throw some light on the subject.

DR. ARTHUR B. HYMAN: In "lymphocytic infiltrate," the lesions are usually on the face. The surface changes are negligible, and the features seen in lupus erythematosus, such as atrophy, hyperkeratosis, and plugging of follicles, are not seen in the so-called lymphocytic infiltrates. The lesion may respond to any of a number of different forms of treatment, including erythromycin, as was just mentioned by Dr. Kesten. It may, however, respond to no form of treatment. It may be very persistent, or clear up spontaneously, so its course is rather different from that of lupus erythematosus. Histologically, in many cases there is a picture distinct from the various phases of lupus erythematosus. Without going into the details of the histologic changes in lupus erythematosus, there are in these cases of "lymphocytic infiltrate" rather well-defined collections of lymphocytes toward the midcutis; the upper cutis and epidermis are almost entirely unaffected. The surface changes characteristically associated with lupus erythematosus clinically as well as histologically are not found here. The upper cutis shows none of the edema associated with lupus erythematosus. What this condition is nobody exactly knows. It seems to be an entity running a different course from that of lupus erythematosus. It may

have many relatives, and among them are the so-called facial granulomas with eosinophiles, true eosinophilic granuloma, the nebulous erythema elevatum diutinum, deep forms of lupus erythematosus, which are very difficult to diagnose without associated, more classic lesions, and true lymphocytoma, which is supposed to show germinal centers almost like lymphoid tissue in the skin. So there is a wide range of conditions to which this may be related, but it still should for the time being be considered something different from lupus erythematosus, and probably it is an entity in itself.

DR. CHARLES S. MILLER: Zones of lymphocytic infiltration are seen in both conditions. In lupus erythematosus other features are prominent such as edema. The edema is away from the areas of the cellular infiltration. The edema in the subepidermic zone produces basal cell disorganization.

DR. PAUL GROSS: I can follow Dr. Hyman's reasoning and would agree that there may be a relationship to the eosinophilic granuloma of the face. On the other hand, I believe that Dr. Jessner is right when he considers lymphocytic infiltration of the skin as an entity, unrelated to the lymphocytoma group.

The spontaneous involution of lymphocytic infiltration has been observed and makes it difficult to evaluate therapy.

The prevalence of lesions on the exposed parts has been noted in most of these cases and makes it more understandable why they have been considered a special type of lupus erythematosus.

DR. GERALD F. MACHACEK: A good deal has been said about differentiation here. We do know, of course, that we have frank cases of lupus erythematosus, discoid variety, that we can pretty well identify both clinically and histologically. It is obvious now that in the last few years there were a certain number of cases that puzzled everyone. We decided there were certain peculiar cases of lupus erythema profundus. Over and above that, someone then described a peculiar entity called actinic dermatosis of the face, which was supposed to be like lupus erythematosus but was not dependent on sunlight. We know that lupus erythematosus is hypergic to sunlight. Now we have another entity, and we are supposed to be able to differentiate one case from the other. On the basis of histology, if not on the basis of clinical appearance, I don't know how you can do it if you have a few lymphocytes. You have got to go over and above this. There is no reason why we could not have a very superficial type of lupus erythematosus without much change in the epidermis. We know in the past we have had a series of cases that looked like lupus erythematosus, particularly in young children on a very one-sided diet who became more or less hypergic to sunlight. On the balancing of the diet, these lesions would disappear. I think Dr. Cipollaro had a number of those small children. You could not differentiate on the basis of histology a few lymphocytes around a few blood vessels. I don't say there are not many different types of conditions, but we have not got criteria where we can say, yes, this is lymphocytic, this is actinic dermatosis, and this is lupus erythematosus. It is very difficult. When we try to be so precise in so unprecise a discipline, I think we are not doing a service to our particular specialty.

DR. JESSE A. TOLMACH: This entity has been studied for a number of years by Dr. Max Jessner. He has found that although it usually simulates lupus erythematosus clinically, it must at times be differentiated from drug eruption, late syphilis, and sarcoid. In this case, it is interesting to note that epithelioma was one of the original provisional clinical diagnoses and that histologic examination revealed its true nature.

Purpura Annularis Telangiectodes (Majocchi's Disease)? Presented by DR. O. CANIZARES.

Patient: A. V. White man, aged 40.

Duration: 10 years.

Location: Ankles and legs.

Description: Irregular, reticulated, brown pigmentation covering the ankles and legs. Some punctate, purpuric elements, few in number, are scattered over the legs. Some of these petechial lesions appear in the perifollicular layer. Some small varicose veins are also visible. The feet show minimal pigmentation and few purpuric lesions.

History: At present the patient is under treatment for hyperthyroidism. Pigmented spots first appeared about the ankles in 1943. It has since spread slowly up the legs and reached the knees about 1950. There has been very little extension of the process since then.

The patient is hospitalized for hyperthyroidism and hyperthyroid heart disease with auricular fibrillation. Treatment of these conditions has not affected the skin condition in any way.

Skin Biopsy: Reported consistent with Majocchi's disease. The epidermis shows slight focal acanthosis, with slight intercellular edema in these foci. The basal cell layer is not disturbed. The papillary and subpapillary layers show slight increase of capillaries. The walls of the capillaries are edematous; the endothelial cells are swollen and in places show degenerative changes. There are small foci of extravasation of red blood cells and also deposits of hemosiderin. There is a minimal amount of perivascular infiltrate. In some areas, the vascular changes extend to the midcutis and even the lower cutis.

DISCUSSION

DR. EUGENE TRAUGOTT BERNSTEIN: I think this is a very typical case. I really enjoyed seeing it. It has all the features of Majocchi, the annular distribution on the lower extremities, and it is now in a state of recession.

DR. ARTHUR B. HYMAN: I have never seen an unquestionable case of Majocchi's disease, so I cannot tell you whether in my opinion it is typical or not. But if this is a case of Majocchi's disease, the lesions are neither annular nor telangiectatic. So the two important features of Majocchi's disease are lacking. In England, one often sees this peculiar kind of mottling on the skin, with nothing telangiectatic about it at all, known as erythema ab igne and due to sitting in front of open fires. Dr. Gross, who has a much longer, wider experience than I, saw cases in Europe, and will I hope tell us what Majocchi's disease really is. In 12 years of assiduous attendance at this and other institutions, I have never seen a case pointed out to me as showing the classic features of what is supposed to me Majocchi's disease. I have grave doubts whether it is an entity different from the hemostatic dermatoses. I am not the first to express this doubt by any means. Recently Kierland (Pigmentary Purpuric Diseases of the Lower Extremities, *M. Clin. N. America*, **35**:457-462, 1951) wrote that the various dermatoses of the legs, including Gougerot-Blum's, Majocchi's, and Schamberg's diseases, angioma serpiginosum, and hemostatic dermatitis (and probably a few others) should all be grouped together as vascular disturbances of the lower limbs, with minor variations of the same essential theme, without further purposeless differentiation. Nevertheless after I shall have heard what Dr. Gross has to say, I might have to withdraw much of what I have just stated.

DR. PAUL GROSS: There is little that can be added to the classic description of purpura annularis by McKee. The telangiectatic punctae, the formation of annular lesions, and the presence of atrophy in the healed central zone are characteristic of this disease. The tendency to ulcerations, which is also mentioned by McKee is rarely seen, but I had occasion to observe it in one patient in whom the lesions tended to break down in hot weather.

The patient presented tonight lacks the features essential for the diagnosis of Majocchi's disease. The eruption is reticulated, pigmented, and purpuric. The patient is a truck driver, and the heat from the motor may account for the resemblance of the eruption to erythema ab igne. The case can be classified as a purpuric pigmented dermatosis but not as purpura annularis telangiectodes.

Regarding the histopathology, I doubt that the capillary aneurysms and endarteritis typical of Majocchi's disease can be demonstrated in the lichenoid and purpuric dermatosis of Gougerot and Blum. We are still in need of further classification of the groups of purpuric dermatoses.

DR. GEORGE M. LEWIS: For rare skin diseases that have been well described and that have been accepted as entities, it is a little late in the day to be saying that one wonders if they occur. Purpura annularis telangiectodes is a well-known condition and has been discussed by competent authorities, men whose opinions we respect. However, I do not agree that this is a case of Majocchi's disease. My impression is erythema ab igne. The absence of atrophy,

little or no purpura, and the fact that the man is driving a truck and sitting near a heater is ample reason for the development of these lesions. While there is a lot of confusion in regard to lesions that are erythematous, purpuric and telangiectatic and have atrophic components, we should make every effort to make a differential diagnosis and resist the temptation to lump them all together. This would indeed be a retrograde step.

DR. ORLANDO CANIZARES: I agree that it is very difficult to make the diagnosis of purpura annularis telangiectodes at the present time. We have been able to follow this patient for some time, and he has presented all the characteristics of this disease at one time or another. The disease is progressive. I do not believe that the heat on the legs which could have been received by driving a truck has any connection with his present complaint, especially since he has changed his occupation a few years ago.

Lichenoid Lesions. Presented by DR. DABNEY MOON-ADAMS.

Erythema Induratum. Presented by DR. JESSE A. TOLMACH for DR. GEORGE H. KOSTANT.

Chronic Nodular Circumscribed Lichenification. Presented by DR. JESSE A. TOLMACH for DR. LEO ORRIS.

Keratosis Follicularis. Presented by DR. E. LADANY and DR. P. MICHAELIDES (by invitation).

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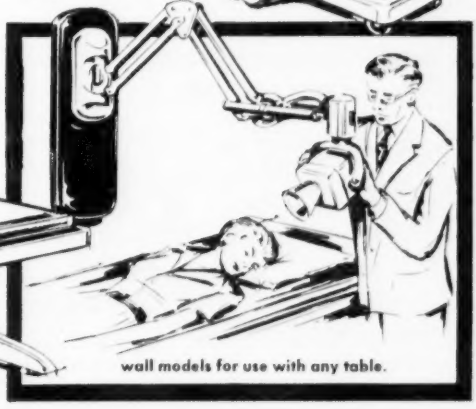

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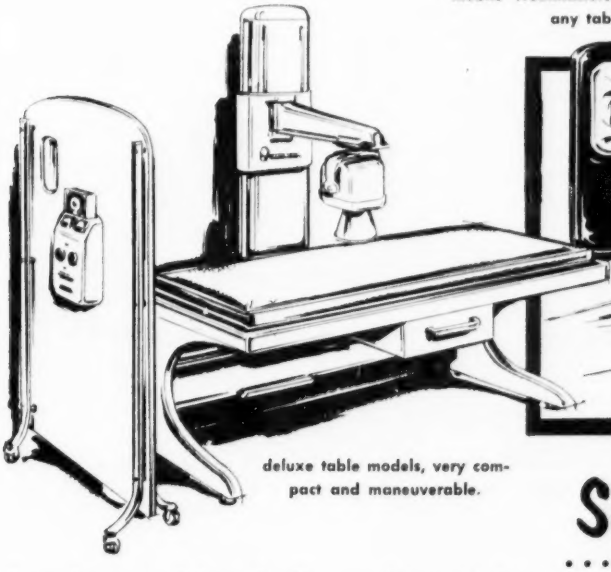

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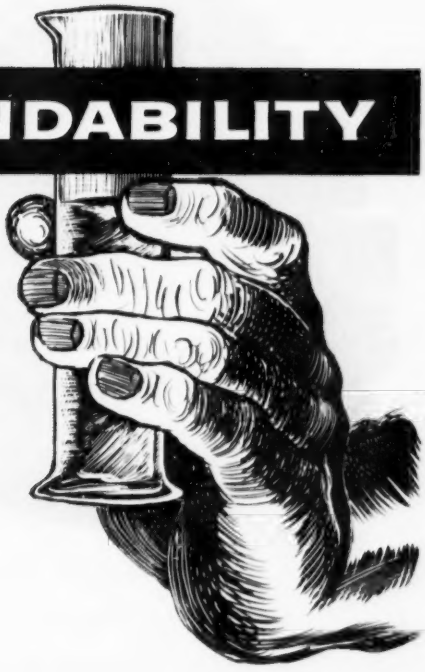

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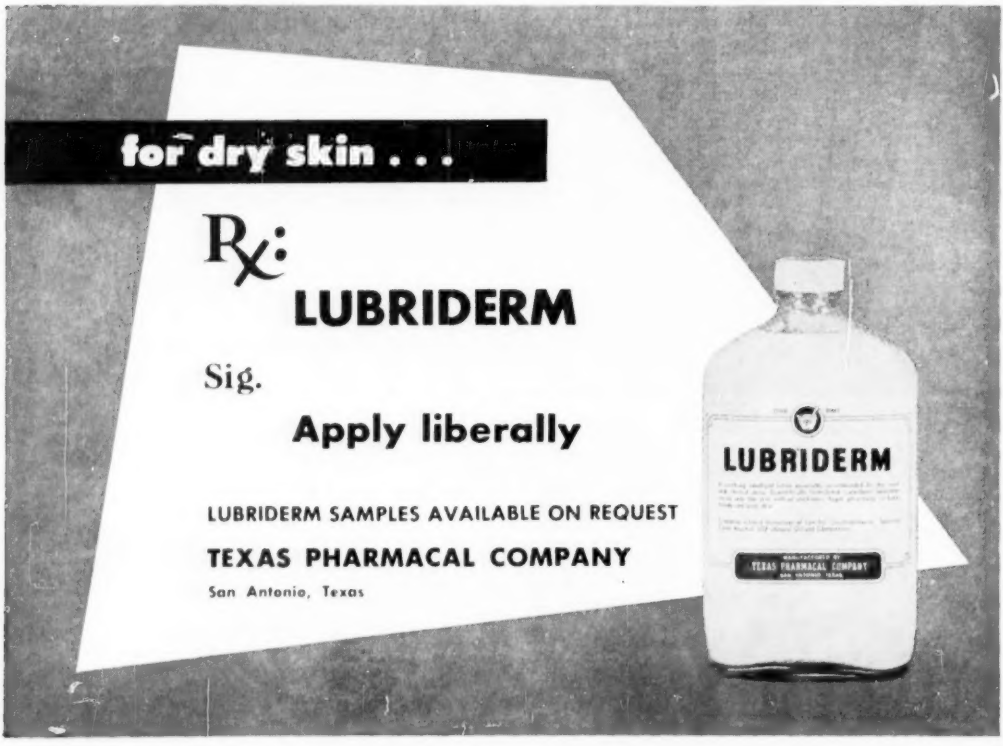

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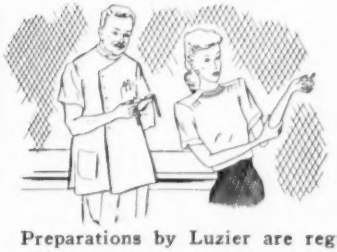

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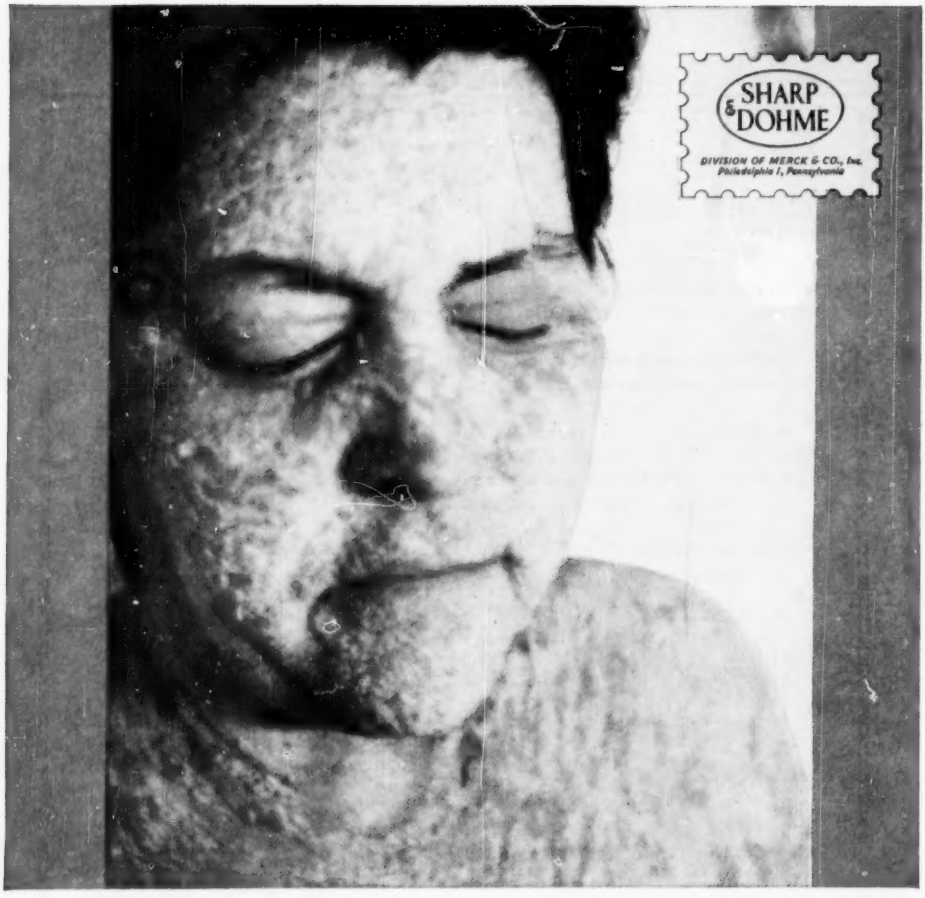

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1. Costello, M. J., *N. Y. State J. Med.* **53**:2075, Sept. 15, 1953. 2. Thorn, G. W., *et al.*, *N. England J. Med.* **248**:632, April 29, 1953.

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